CORRELATION OF DOSE TO BONE MARROW WITH HEMATOLOGICAL TOXICITY AND MRI BASED ESTIMATION OF CONVERSION OF ACTIVE TO INACTIVE BONE MARROW IN LONG COURSE CHEMO- RADIATION FOR LOCALLY ADVANCED RECTAL CANCER

DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY
EXAMINATION APRIL 2015

TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI - 600032.

Certificate

I Jayant J Bhargav, a post graduate registrar in the department of Radiotherapy, Christian Medical College, hereby declare that the dissertation entitled "**CORRELATION OF DOSE TO BONE MARROW WITH HEMATOLOGICAL TOXICITY AND MRI BASED ESTIMATION OF CONVERSION OF ACTIVE TO INACTIVE BONE MARROW IN LONG COURSE CHEMO-RADIATION FOR LOCALLY ADVANCED RECTAL CANCER** " is a bonafide work done by me. This is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Radiotherapy (Branch IX) examination conducted in April 2015.

DR JAYANT J BHARGAV

POST GRADUATE REGISTRAR

DEPARTMENT OF RADIOTHERAPY

CHRISTIAN MEDICAL COLLEGE

VELLORE

Certificate

This is to certify that the dissertation entitled "**CORRELATION OF DOSE TO BONE MARROW WITH HEMATOLOGICAL TOXICITY AND MRI BASED ESTIMATION OF CONVERSION OF ACTIVE TO INACTIVE BONE MARROW IN LONG COURSE CHEMO- RADIATION FOR LOCALLY ADVANCED RECTAL CANCER** " is a bonafide work done by Dr. Jayant J Bhargav, Post Graduate Registrar in the Department of Radiotherapy, Christian Medical College, Vellore during the period from June 2013 to April 2015 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination conducted in April 2015.

Principal

Christian Medical College

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Head of the Department

Dr.Selvamani B

Professor & Head

Department of Radiotherapy

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Vellore, India - 632004

Certificate

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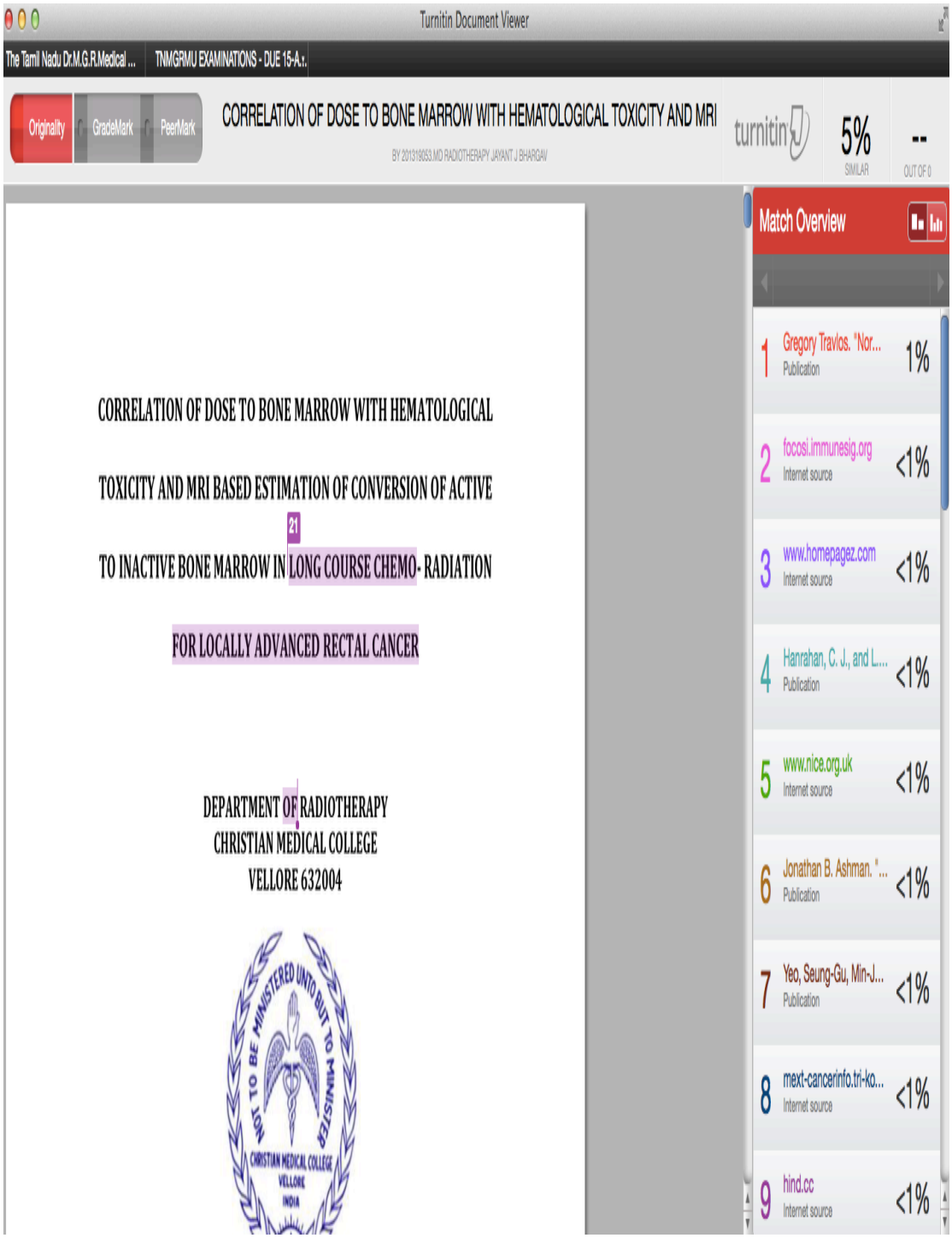
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May 08, 2014

Dr. Jayant J. Bhargav
PG Registrar
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Sub: **Fluid Research grant project:**
Prospective Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo- radiation for Locally advanced Rectal cancer.
Dr. Jayant J Bhargav, PG Registrar, Dr. Thomas Samuel Ram, Dr. Selvamani, Dr. Anuradha Chandramohan, Dr. Anu Eapen, Radiodiagnosis, Dr. B. Antonisamy, Biostatistics, CMC, Vellore, CMC.

Ref: IRB Min No: 8650 [OBSERVE] dated 19.02.2014

Dear Dr. Jayant J. Bhargav,

The Institutional Review Board (Blue, Research and Ethics Committee) of the ChristianMedical College, Vellore, reviewed and discussed your project entitled "Prospective Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo- radiation for Locally advanced Rectal cancer." on February 19, 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Jayant J Bhargav, Thomas Samuel Ram, Selvamani, Anuradha Chandramohan, Anu Eapen, B. Antonisamy.
3. Informed Consent form
4. Information sheet
5. No of documents 1-4

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
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The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on February 19, 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMCH.	Internal, Clinician
Dr. J. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Ranjith K Moorthy	MBBS M Ch	Professor, Neurological Sciences, CMCH.	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMCH.	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, Ph D, MAMS	Professor, Cardiology, CMCH.	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC	Internal, Clinician
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC	Internal, Clinician

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Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMCH	Internal, Legal Expert
Dr. Shirley David	M.Sc, PhD	Professor, Head of Fundamentals Nursing Department, CMCH	Internal, Nurse
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Dr. Denise H. Fleming	B. Sc (Hons), PhD	Honorary Professor, ClinicalPharmacology, CMCH.	Internal, Scientist & Pharmacologist
Dr. Vathsala Sadan	M.Sc, PhD	Professor, Community Health Nursing, CMCH.	Internal, Nurse
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMCH.	Internal, Clinician
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), CMCH. Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

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Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Glas) (EDIN)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 48,980/- INR (Rupees Forty Eight Thousand Nine Hundred and Eighty only) will be granted for 11 months.

Yours sincerely

CHRISTIAN MEDICAL COLLEGE VELLORE INDIA

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Cc: Dr. Thomas Samuel Ram, Radiation Oncology, CMC

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Ref: IRB-A1-19.02.2014

July 24, 2014

Dr. Jayant J Bhargav
PG Registrar
Department of Radiation Oncology
Christian Medical College,
Vellore 632 004

Ref: IRB Min. No. 8650 dated 19.02.2014

Dear Dr. Jayant J Bhargav,

The Institutional Review Board (Blue, Research and Ethics Committee) of the ChristianMedicalCollege, Vellore, reviewed and discussed the following amendments for the study titled "Prospective Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo-radiation for Locally advanced Rectal cancer." on July 24th 2014.

1. Change of title from "Prospective Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo- radiation for Locally advanced Rectal cancer' to Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo- radiation for Locally advanced Rectal cancer.
2. Revised Summary
3. Revised Research Plan
4. Revised Budget

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on July 24th 2014 at 9.45 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Dr. Alfred Job Daniel	D Ortho, MS Ortho, DNB Ortho	Principal, Chairperson-Research Committee, IRB, CMC, Vellore	Internal, Clinician

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Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
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Additional Vice Principal (Research)

Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psych MA(Theology), Dr. Min(Clinical Cour	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External,
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Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
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Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMC, Vellore	Internal, Clinician
Mrs. Sheela Durai	M Sc Nursing	Addl. Deputy Nursing Superintendent, Professor of Nursing in Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

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Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), CMCH, Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the above amendments as presented.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Thomas Samuel Ram, Radiation Oncology, CMC, Vellore

ACKNOWLEDGEMENT

I would like to express my heartfelt gratitude to my mentor and guide Dr Thomas Samuel Ram without whose help , this work would not have been possible. His ‘out of the box’ thinking never fails to impress and inspire me. His constant support and guidance, his willingness to help at any time of the day(or night) are things that I deeply appreciate.

I would like my express my sincere gratitude to Professor Dr Selvamani B , Head of Department, for being a limitless source of support and encouragement. Her remarkable ability to multitask, her genuine interest in providing and maintaining the highest quality of medical care in the clinic, is truly inspiring.

I am grateful to Dr Anuradha, Department of Radiodiagnosis, for her endless patience and dedication. The seemingly endless hours of work she has put in, without as much as even a frown, is something that I deeply appreciate.

I would like to thank Mr Timothy, Mr Shivashakthi, Department of Medical physics and Dr Rajeev, Department of Radiodiagnosis, for their valuable contributions.I would like to thank Dr B Antonisamy and his associates for providing their statistical expertise.

Lastly, I would like to express my sincere gratitude to my parents and sister, for their valuable support and encouragement.

Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo- radiation for Locally advanced Rectal cancer.

Table of Contents

TITLE: CORRELATION OF DOSE TO BONE MARROW WITH HEMATOLOGICAL TOXICITY AND MRI BASED ESTIMATION OF CONVERSION OF ACTIVE TO INACTIVE BONE MARROW IN LONG COURSE CHEMO- RADIATION FOR LOCALLY ADVANCED RECTAL CANCER

DEPARTMENT: RADIOTHERAPY

NAME OF THE CANDIDATE: JAYANT J BHARGAV

DEGREE AND SUBJECT: MD RADIOTHERAPY(BRANCH IX)

NAME OF THE GUIDE: THOMAS SAMUEL RAM

Aims : To correlate the dose to bone marrow with the incidence and grade of hematological toxicity and to estimate the extent of inactivation of bone marrow in patients with locally advanced rectal cancer undergoing neo adjuvant long course chemoradiation.

Methods and materials: 20 patients with locally advanced rectal cancer were enrolled for the study after clearance from the institution review board. All the patients received preoperative long course radiotherapy using 3D conformal modality to a dose of 50.4Gy.They received concurrent chemotherapy with daily Capecitabine (825mg/m2). The entire pelvis was contoured on the simulation CT, the active marrow (red) bone marrow was delineated on both the pre radiotherapy as well as the post radiotherapy MRI of the pelvis on the T1 weighted images. Baseline and weekly blood investigations were recorded during the course of therapy. The dosimetric parameters such as V5, V10, V20, V30 and V40 were correlated with the incidence of Grade 3 or more hematological toxicity. The pre and post radiotherapy volumes of the active marrow and the extent (in percentage volume) of inactivation of bone marrow (red to yellow marrow conversion) due to LCCRT was also documented. The Shapiro Wilk/Mann Whitney test was used to correlate the bone marrow dose with toxicities and the paired T test was used to test the significance of conversion of active to inactive marrow.

Results: The incidence of grade 3 or more toxicity of hemoglobin correlated with V30 and V40 values(p value 0.02 and 0.0095 respectively). The toxicity grades of the other blood elements however did not show any correlation with any of the dosimetric variables. The median value of the pre radiotherapy active marrow was 346.21cc and the median of the post radiotherapy active marrow was 116.44cc.The percentage inactivation after therapy had a median value of 57.64% (range 38.98% - 83.39%)There was also a significant conversion of active to inactive bone marrow as detected on the MRI, the correlation of the pre and post neoadjuvant chemoradiotherapy marrow volumes was highly significant (p value <0.0001)

Conclusion: The volume of pelvic bone marrow receiving at least 30Gy or more in patients undergoing long course chemoradiotherapy for locally advanced rectal cancer has a significant impact on anemia. There was also a significant conversion of active to inactive bone marrow as detected on the MRI. The significant myelosuppression associated with the use of both chemotherapy and radiotherapy in the management of rectal cancer warrants efforts to limit the toxicity to the bone marrow. The use of MRI

and other functional imaging for visualization and delineation of the bone marrow and its use in radiotherapy planning is now providing possibilities to further limit normal tissue toxicity

Keywords: Locally advanced rectal cancer, neoadjuvant chemoradiotherapy, Long course chemoradiotherapy, bone marrow, bone marrow sparing radiotherapy, MRI in radiotherapy

Introduction

Colorectal cancer is emerging as a major cancer burden with the increase in incidence and mortality, both globally as well as in India (1). Neoadjuvant long course chemoradiation therapy and Total Mesorectal Excision (TME) is the current standard of care in locally advanced rectal cancer (2).Following surgery, patients receive adjuvant chemotherapy based on the findings of the surgical pathology(3).It is well known that both radiotherapy and chemotherapy leads to significant myelosuppression. With the availability of CT based planning several authors have attempted to document the dose to bone marrow and correlate the hematological toxicity by studying the dose volume histogram(4) (5). There is not enough literature at present evaluating the degree of myelosuppression and the extent of bone marrow damage caused by neo adjuvant chemoradiotherapy. This study is undertaken to estimate the incidence and degree of hematological toxicity, which could be, attributed to chemoradiotherapy and objectively estimate the extent of bone marrow injury.

Aims and Objectives

-1. To correlate the dose of radiation received by the bone marrow(volume of the marrow receiving a specified dose) and the incidence of grade 3-4 hematological toxicity in patients undergoing Long course chemoradiation for locally advanced rectal cancer.

-2. To estimate the extent of inactivation of bone marrow caused following completion of long course chemoradiation using an MRI based delineation of the marrow

Review of literature

Epidemiology

Colorectal cancer continues to be a major global burden in terms of the incidence and the morbidity. Worldwide, Colorectal cancer is the third most common malignancy affecting men and the second most common malignancy affecting women(6).Globally cancers of the anorectum constitute more than 40% of the total colorectal cancers noted. Though the incidence of rectal cancer in India is much lesser than that in developed world, it is on a definite increasing trend. In India, when both genders are taken together, it ranks fifth in terms of incidence and sixth in terms of mortality(7). The estimated age standardized incidence rate (ASR) of rectal cancer in India is 7.19 and 5.08 per 100,000 in males and females respectively (1).

Of particular importance is the observation that there has been an increased number of younger (with a mean age of 40-45 years) patients from West Bengal, the North Eastern states as well as from Bangladesh, being diagnosed with colorectal cancer (8) (9).

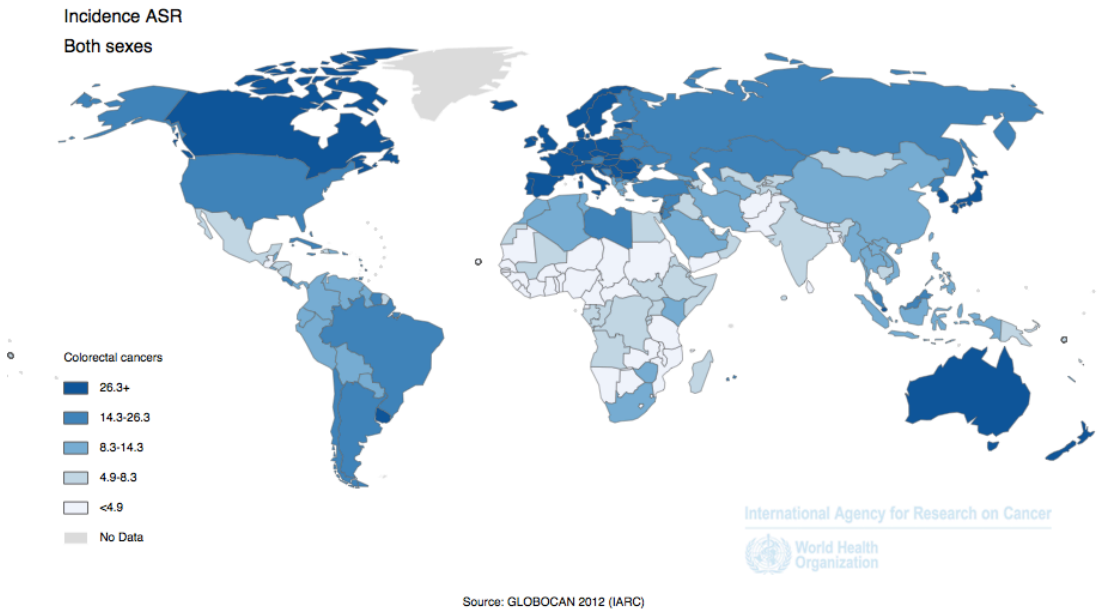


Figure 1: Worldwide incidence of colorectal cancers (ASR)

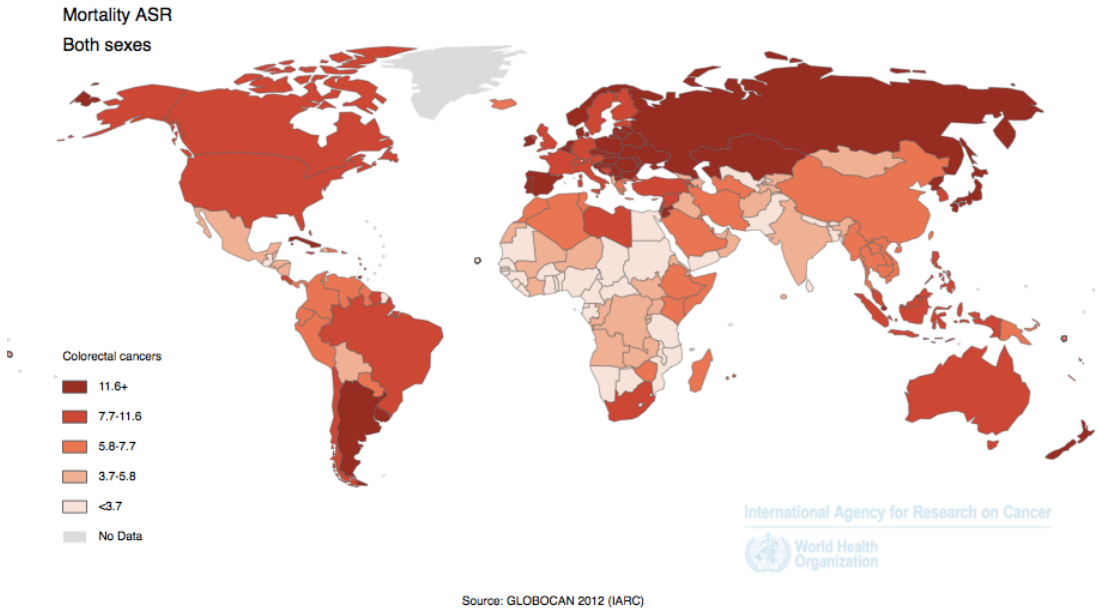


Figure 2: Worldwide mortality rates of colorectal cancers (ASR)

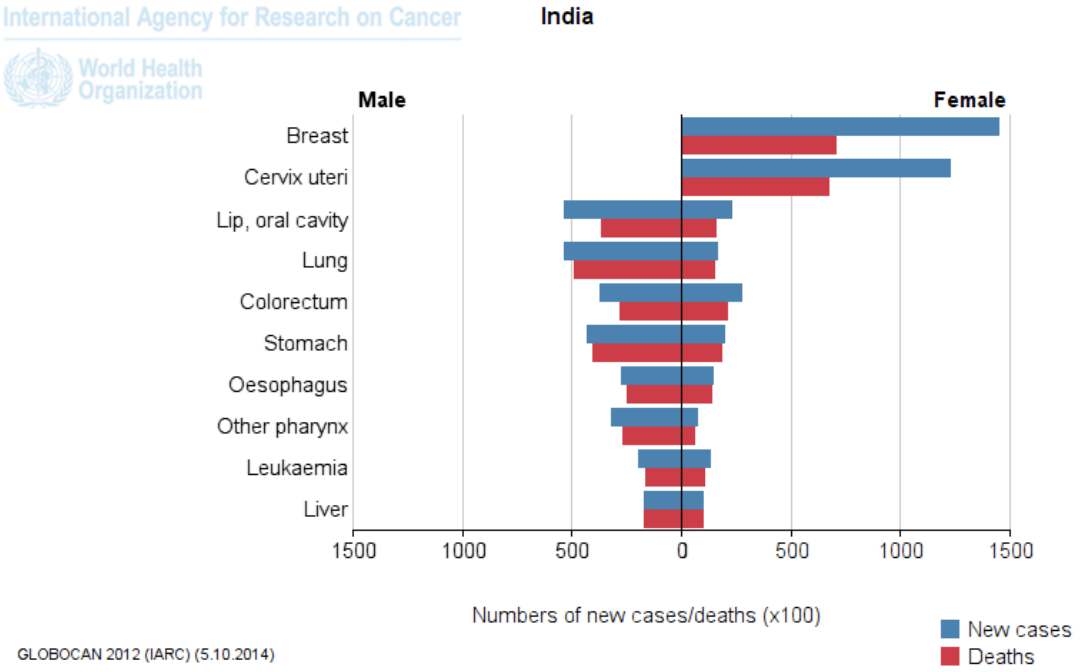


Figure 3: Ten leading cancers in the Indian population

India
Colorectum

Year	Estimated number of new cancers (all ages)	Male	Female	Both sexes
2012		36917	27415	64332
	ages < 65	23015	17812	40827
	ages >= 65	13902	9603	23505
2015		39904	29851	69755
	ages < 65	24936	19187	44123
	ages >= 65	14968	10664	25632
	Demographic change	2987	2436	5423
	ages < 65	1921	1375	3296
	ages >= 65	1066	1061	2127

GLOBOCAN 2012 (IARC) - 5.10.2014

Figure 4: Predicted incidence of colorectal cancers in the Indian Population in the year 2015.

Risk Factors

The risk factors associated with rectal cancer can be grouped into two categories

1)Non modifiable risk factors

a) Age: More than 90% of colorectal cancer occurs in patients aged 50 or more. The likelihood of diagnosis of rectal cancer progressively increases after the age of 40,and sharply after the age of 50 (10).However, the number of younger patients being diagnosed with colorectal cancer, especially in our country, has steadily been increasing (1)

b) History of adenomatous polyps: Neoplastic polyps of the colorectum are precursor lesions of colorectal cancer (11). Most of the sporadic colorectal cancers develop from the pre existing villous or tubular adenomas. The development of a malignancy from an adenoma has a long latency of about 10 years (12). Detection of and removal of the precursor prior to malignant transformation may reduce the risk of invasive colorectal cancer (13).

c) History of Inflammatory bowel disease: Ulcerative colitis and Crohn's disease both increase the risk of developing colorectal cancer later in the life (11). This warrants the adoption of screening earlier when compared to the general population.

d) Family history of Colorectal cancer or adenomatous polyps: There is a high risk among first-degree family members of patients diagnosed with colorectal cancer and adenomatous polyps. Approximately 20-25% of colorectal cancers are detected among the first-degree family members. (14) (15)

d) Predisposition due to genetic syndromes: 5 and 10% of Colorectal malignancies are detected in people with genetic syndromes, such as FAP and the syndromes of Gardner, Lynch and Turcot.

2) Modifiable risk factors

Modifiable risk factors of colorectal cancers include smoking, physical inactivity, obesity, eating processed meat and excessive alcohol (16) (11)

Anatomy

There is considerable variation and ambiguity regarding the anatomical definition of the rectum due to differing anatomical and surgical landmarks. For surgical and oncological considerations the anatomy of the rectum is simplified as follows:

The rectum is divided into three parts. The lower rectum is approximately 3 to 6cm from the anal verge. The mid rectum is from 5-6 cm to 8-10 cm. The upper rectum is from 10 cm to 12-15 cm from the anal verge.

The location of the tumour is usually specified in terms of the distance from the anal verge. Occasionally it may be specified based on the dentate line or the anorectal ring. The reference anatomical landmark from which the measurements are made, have to be clearly mentioned. Likewise, the method of measurement; per rectal examination, colonoscopy, flexible endoscopy has to be mentioned.

The location of the tumour has considerable implications in the prognosis and selection of appropriate therapy. The upper third of the rectum is envisaged by the peritoneum anteriorly and laterally. The middle third is lined by the peritoneum on the anterior aspect only. The lower third of the rectum, which is in close proximity to other pelvic structures, is completely devoid of peritoneal covering.

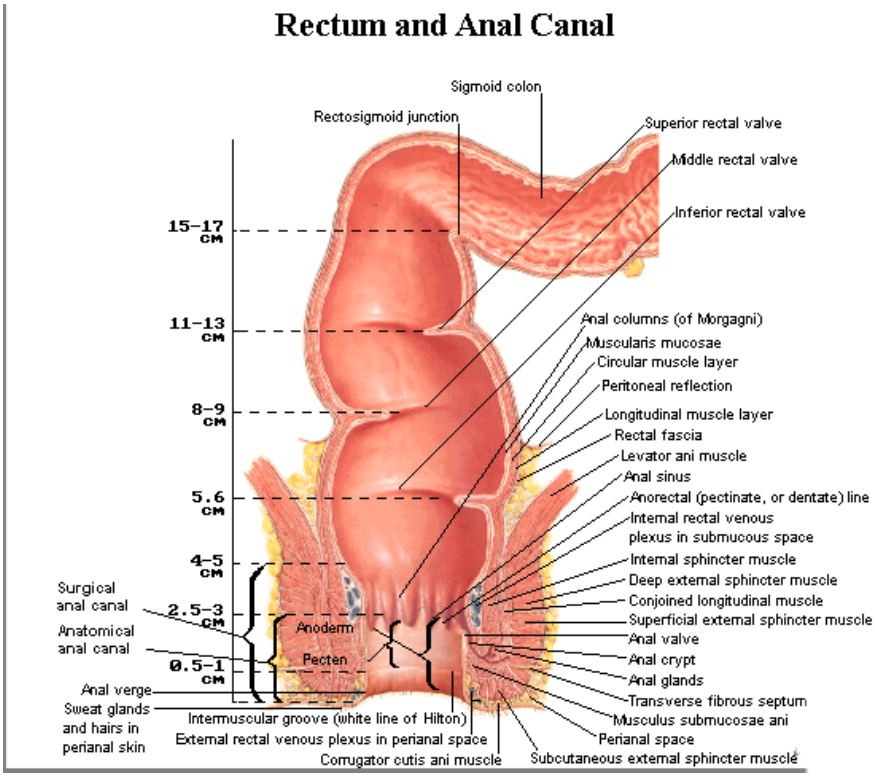


Figure 5: Surgical anatomy of Rectum and Anal canal

The majority of the lymphatic drainage of the rectum passes along the superior hemorrhoidal artery. The para rectal nodes above the level of the middle rectal-valve drain along the superior hemorrhoidal lymphatic chain. The lymphatics below the level of the middle rectal valve pass to nodes along the middle hemorrhoidal artery, obturator fossa, hypogastric and common iliac arteries. The rectovaginal septum,Denonvillier's fascia and the mesorectum has extensive lymphatic supply.

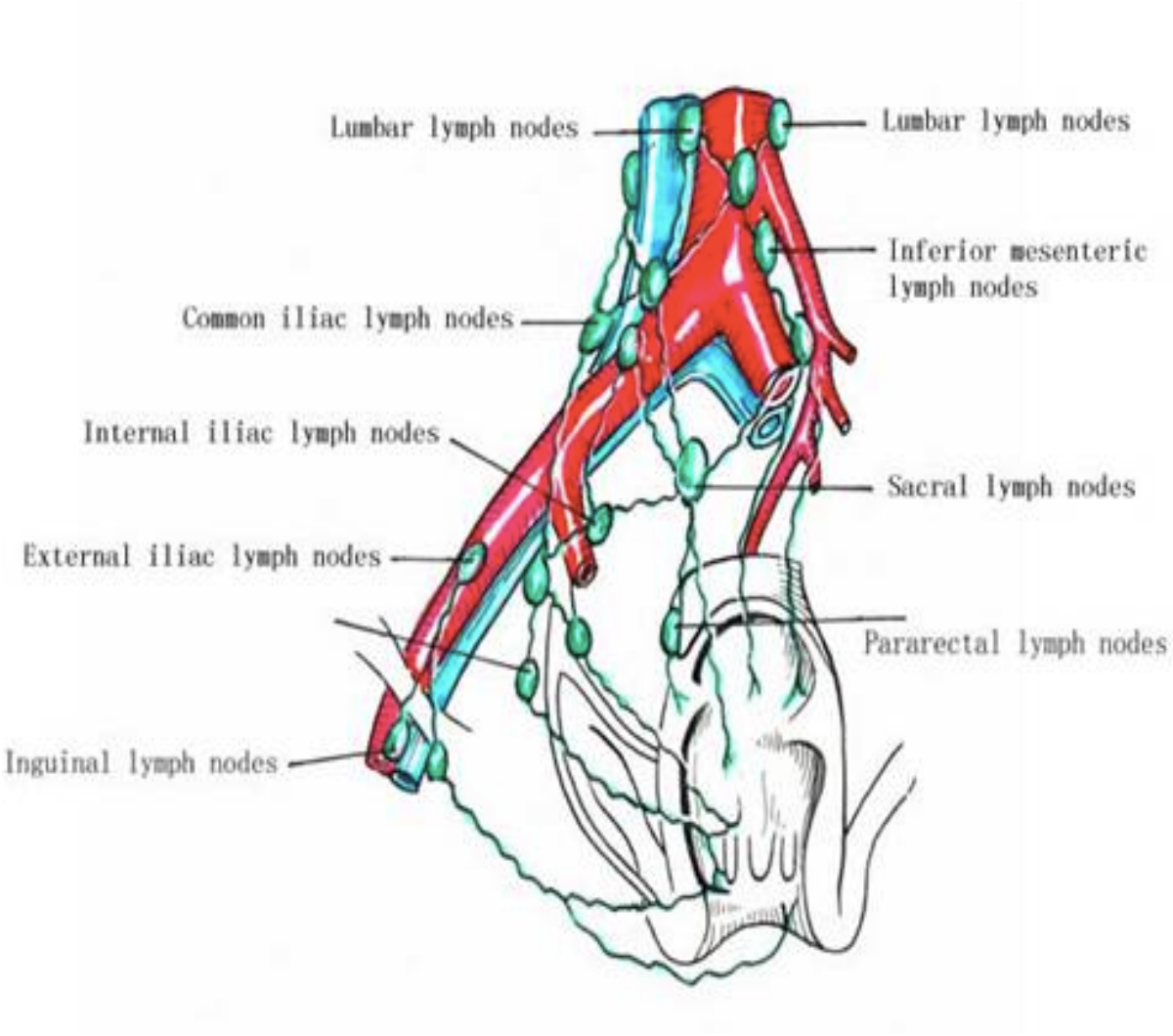
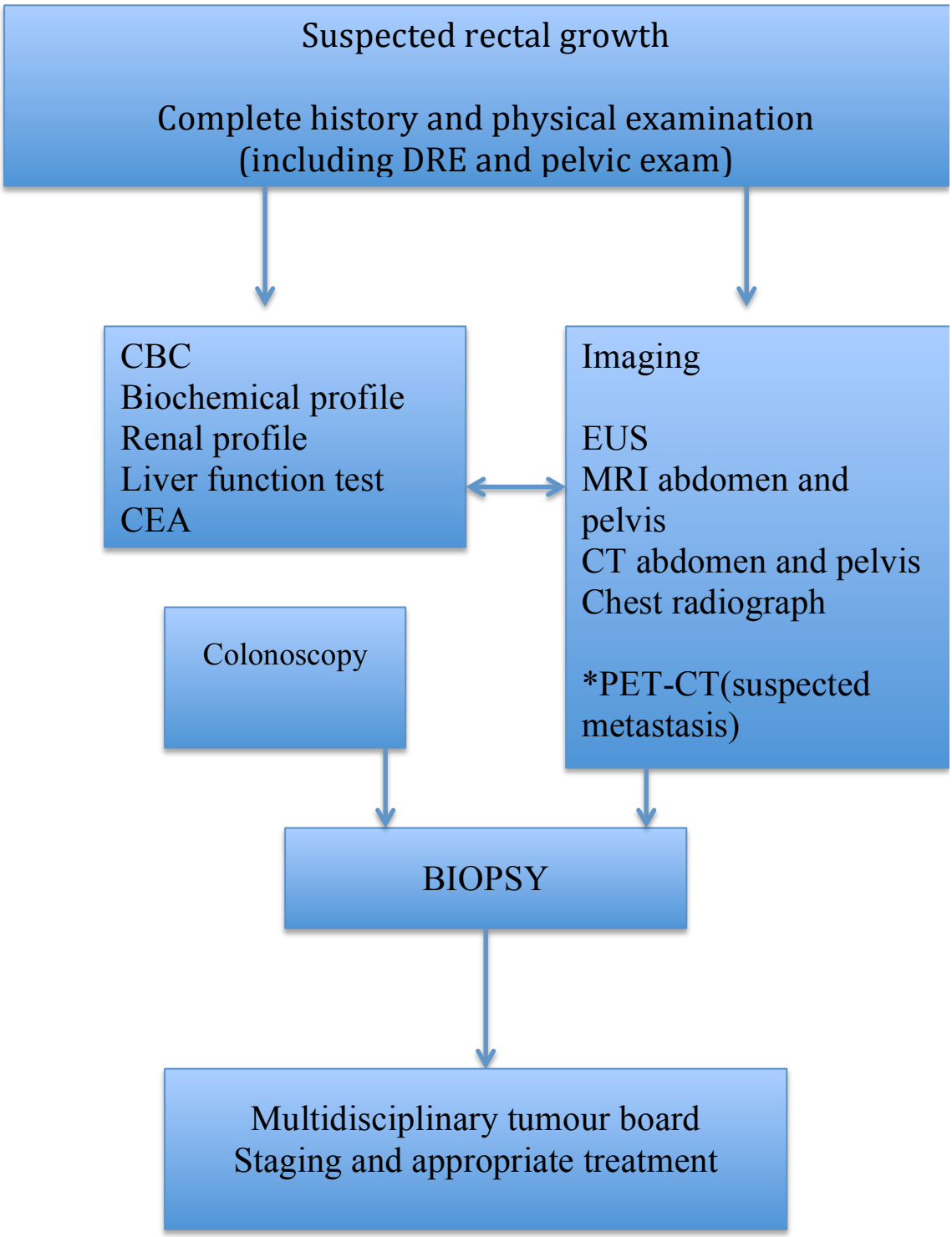


Figure 6: Lymphatic drainage of the rectum

Management of rectal cancer



Work-up

The work up of a patient with a suspected rectal growth includes a history, physical examination including a per rectal examination, complete blood cell count, liver function tests, renal function test and a baseline CEA.

Colonoscopy or barium enema to evaluate the large intestine for polyps, synchronous growths is often needed.

Imaging studies include a CT or MRI of the abdomen and pelvis for accurate delineation of the tumour as well as to rule out metastasis in other abdominal organs. MRI of the pelvis with or without the endorectal coil is considered to be more superior in visualization of the tumour extent compared to a CT pelvis (17).A PET-CT would be warranted in some scenarios to help in exclusion of distant metastasis. It is, however more useful in cases of a recurrent or a suspected recurrent growth (18).The Endocrectal Ultrasound is considered to be the imaging modality of choice for accurate T staging of the growth (19). A chest radiograph or a CT thorax is warranted to rule out lung metastasis.

A biopsy of the growth is essential and may be done at the time of the colonoscopy/sigmoidoscopy or as a guided procedure using endorectal ultrasound or CT to help in localization of the tumour.

The staging of patients with rectal cancer is carried out based on the TNM staging based on the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging systems (20).The older Dukes's classification and the Modified Aster Coller classification is seldom used nowadays.

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[a]
T4b	Tumor directly invades or is adherent to other organs or structures[a,b]
Regional Lymph Modes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in two to three lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolorectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site
M1b	Metastasis in more than one organ/sit or peritoneum

Figure 7: AJCC TNM staging (2009)

	American Joint Committee on Cancer[a]				
Stage	T	N	M	Dukes[b]	MAC[c]
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	–	D
IVB	Any T	Any N	M1b		

Figure 8: AJCC stage grouping

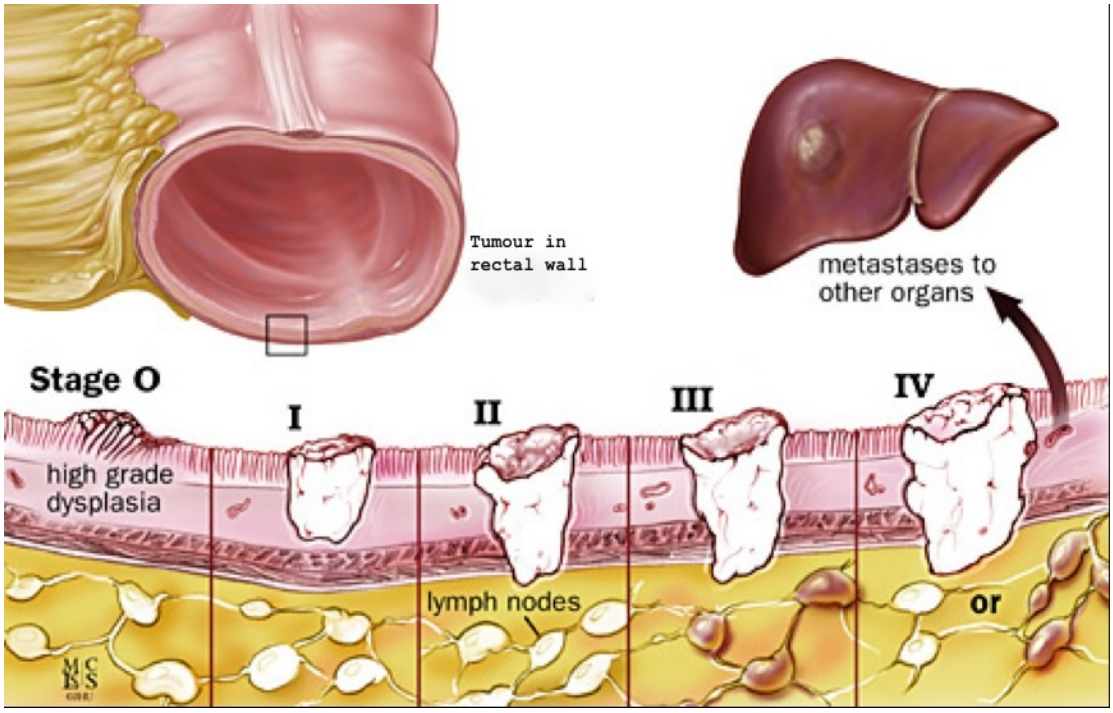


Figure 9: Representation of different stages of rectal cancer in terms of depth of invasion

Prognostic factors affecting outcomes

1) *Tumour location*

Tumors above the anorectum drain to the internal iliac lymph nodes and have a propensity to metastasize to the liver via the portal drainage; those below it drain into the nodes along the inferior rectal and external iliac pathways and may metastasize to the lungs via the caval drainage.

Overall, distal tumours have a worse prognosis than the proximal growths(21)(22).

2) *Tumour stage*

Tumour staging based on the AJCC or the UICC systems remains the dominant factor in determining prognosis(23).

3) *Histopathological factors*

Histology such as signet ring cell type or melanomas have a poorer prognosis(24).Higher grade of the tumour (poorly differentiated)tumours are associated with poorer prognosis.Lymphovascular invasion is also considered to be an independent factor and the presence of which indicates poorer prognosis(25)(26).

4) *Tumour fixation*

Tumours which are fixed tend to have poorer surgical outcomes which in turn translates into poorer local control and survival outcomes(27)(28)

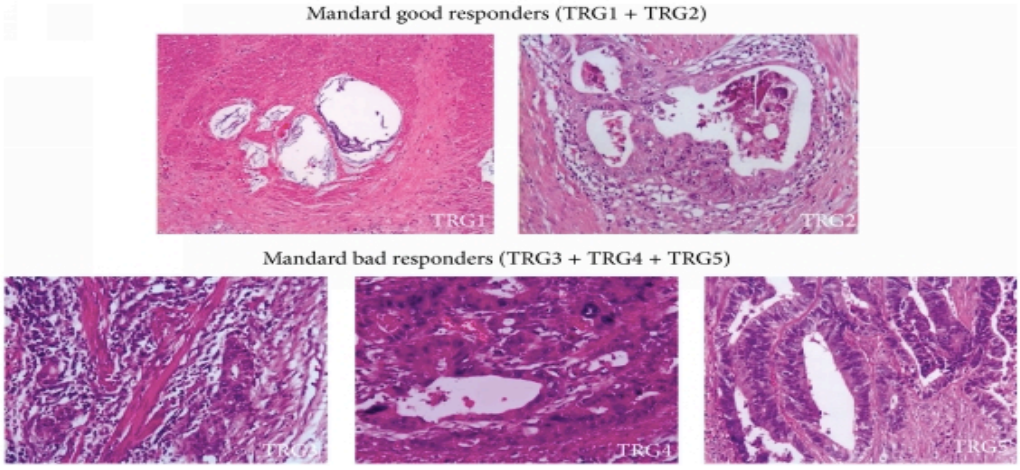
5) *Circumferential involvement*

Circumferential involvement of the tumours may lead to partial or complete luminal obstruction. These tumours are found to have a higher incidence of lymph nodal metastasis and portend a poorer prognosis. (29)(25)(30)

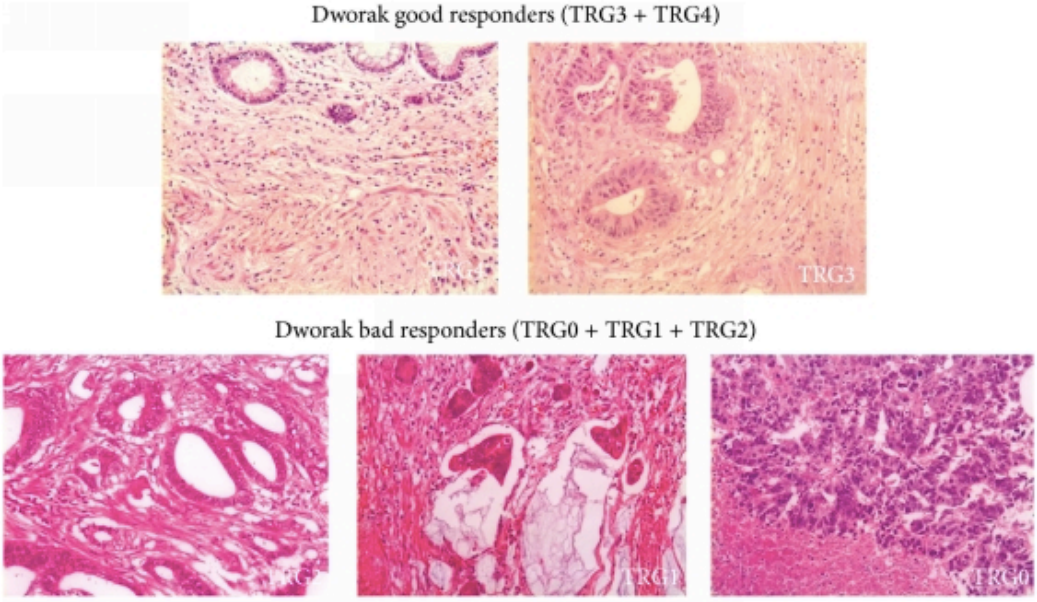
6) *Degree of Tumour regression*

The routine use of neo adjuvant therapy for locally advanced rectal cancer has led to the development of grading systems based on the extent of tumour regression.

Though different grading systems are used, the most commonly used are the Mandard and the Dworak systems. Higher grades of regression after neo adjuvant therapy have a better prognosis (31)(32)(33)(34).



Mandard TRG system	
TRG1	No viable cancer cells, complete response
TRG2	Single cells or small groups of cancer cells
TRG3	Residual cancer outgrown by fibrosis
TRG4	Significant fibrosis outgrown by cancer
TRG5	No fibrosis with extensive residual cancer



Dworak TRG system	
TRG0	No regression
TRG1	Dominant tumor mass with obvious fibrosis and/or vasculopathy
TRG2	Dominant fibrotic changes with few tumor cells or groups (easy to find)
TRG3	Very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucus substance
TRG4	No tumor cells, only fibrotic mass (total regression)

Figure 10: Tumour regression grading systems

Therapeutic options

Surgery

Surgery has always been the mainstay of treatment in rectal cancers. Early efforts at surgery mainly involved wide local excision of tumours. The surgical options included:

Local Excision

a)Trans anal approach:

This approach offers the least morbidity among surgical options. Mainly employed for tumours that are less than 8cm from the anal verge. Tumours that are more proximal cannot be approached using this technique.

*b)*Trans-Sphincteric(York Mason) approach*:*

The entire anal sphincter is divided in the midline. Used for tumours near the anorectal region.

c) Posterior para sacral (Kraske) approach*:*

A para sacral longitudinal excision from the just above the anus to the inferior aspect of the glueus maximus allows a full thickness excision of proximal growth.

A complete resection requires excision of the entire thickness of the growth into the fat. The entire growth has to be removed in one uninterrupted specimen, so that the pathologist is enabled to give a better description of the margins in relation to the tumour. The major limitation of the above mentioned approaches is the fact that lymph nodal sampling or excision is not possible. It was noted that that the incidence of nodal metastasis in T1 lesions was in the range of 5-10%. But, for T2 it was noted to be as high as 20-35% (35).This high rate of lymph nodal metastasis, makes local excision unsuitable for T2 lesions. Local excision for even favourable T2 and rarely T3 lesions followed by adjuvant therapy has yielded unfavourable results.

At present, local excision is recommended for small growths that are usually less than four centimetres, less than 8-10 cm from anal verge, clinically T1 or occasionally, favourable T2 lesions. They are usually well to moderately differentiated mobile lesions that occupy less than 40% of the circumference. It is also not recommended in case of adverse pathological findings like ulceration or lymphovascular invasion (36) (37).

Other locally advanced rectal growths necessitate the need for different surgical options.

Historically, excisions with generous 5cm margins both proximally and distally were attempted. The intramural spread of tumour was rarely beyond 1.5cm. 2cm proximal and distal margins were attempted with acceptable results. Some of the more recent studies have indicated that 1cm proximal and distal margins seem to offer equivalent

results, while offering the advantage and possibility to proceed with a sphincter saving surgery (38) (39).

Low anterior resection

Low anterior resection (LAR) offers a sphincter sparing surgical excision, while not compromising of the local or distant recurrence rates (40). The possibility of saving the sphincter reduces with the more distal location of the tumour.

LAR is now being performed for upper third as well as the middle third and in some lower third growths as well (41). A pre operative assessment of the sphincter tone, body habitus and pelvic anatomy is a must for selecting the appropriate patient for the procedure. The use of circular stapling devices and the need for modest 1-2cm margins has vastly increased the adoption of this approach.

In patients planned to undergo LAR following neo adjuvant radiotherapy, it is advisable to mobilize the splenic flexure so that an unirradiated loop of bowel may be later used for the anastomosis. The advantage of the LAR, being the possibility of sparing the sphincter, with a resultant better quality of life due to the lack of a colostomy, is sometimes compromised by the post operative complications of poor sphincter control, bowel urgency and frequency (42).

Abdominoperineal resection

The abdominoperineal resection (APR) has historically been the gold standard for distal rectal tumours. It entails a proctectomy with the need for a permanent colostomy.

The anatomy of the pelvis, the proximity to the prostate or the vagina and the thin mesorectum has a considerable bearing of the margins achieved following surgery (43). APR in general has more morbidity compared to the LAR. It also suffers from the fact that patients report a lower quality of life due to the presence of the permanent colostomy (44).

Worldwide there has been a decrease in the adoption of this approach even for the distal tumours (45).

Total Mesorectal excision

Following a standard LAR or APR the local recurrence rates were found to be in the range of 15-30%. The high rate of recurrence is probably due to the fact that the lateral spread of the tumour spread is not just at the level of the tumour, but all through the mesorectum. The standard approaches did not address the same. It was noted that local recurrence rates reduced when there was an enbloc removal of the tumour along with the endopelvic fascia encompassing it. Total mesorectal excision (TME) entails a sharp dissection along the plane to separate the visceral and the parietal layers of the endopelvic fascia so that the entire rectal growth along with the entire mesorectum is excised out in one uninterrupted gross specimen (46). Surgical expertise has a considerable influence on the margins attained and the resultant local and distant recurrence rates (47). This approach enables the attainment of a better radial margin compared to the other surgical approaches. It is recommended that a minimum of 12-15 nodes be excised for complete pathological staging (48). TME, although associated with slightly higher rates of complications such as anastomotic

leak and delay in wound healing, leads to a higher rate of local control. This has since then, become the standard approach in patients undergoing excision.

TME both open as well as using a laparoscopic approach resulted in similar oncological outcomes (49).

Recent surgical advances employing extra levator APR, laparoscopic approaches for TME, ultra low LAR and robotic LAR and TME are in different phases of validation. The above approaches all have a common drawback in being available only in a few centres worldwide, the adoption of the same in other centres has been slow due to the associated cost and long learning curves (47).

Adjuvant therapy

The local failure rates after surgery alone was as high as 25-30% (50).This unacceptable rate of local failure necessitates the need for adjuvant therapies to provide better local and distal control.

Surgery followed by radiotherapy alone

Post operative radiotherapy requires the use of larger radiation portals in order to encompass the perineal scar in patients who have undergone an APR. Regardless of the surgical approach, there were concerns of using radiotherapy alone due to the larger small bowel volumes and the potentially hypoxic tumour bed leading to perceived poorer outcomes.

Surgery alone versus surgery followed by adjuvant radiotherapy were compared; the use of radiotherapy led to a reduced local failure rates, but had no effect on the disease free survival or overall survival rates (50) (51).

Local failure rates after adjuvant radiotherapy alone, though marginally better, were still unacceptably high.

Surgery alone versus surgery followed by adjuvant chemotherapy

Though, as a part of larger trial, the arm that employed post operative chemotherapy alone showed a high rate of local failure in the range of 10-15% regardless of the regimen used (51).

In view of the above results, efforts were made to combine radiotherapy and chemotherapy in the adjuvant setting.

Surgery alone versus surgery followed by chemoradiotherapy

As the treatment modality in one of the arms in large trials, adjuvant chemoradiotherapy showed increase in the disease free survival as well as overall survival (52) (53).Though the use of adjuvant combined chemoradiotherapy led to significant improvements in disease free survival and overall survival, there was an associated increase in the toxicity compared to the arms using adjuvant chemotherapy or radiotherapy alone (52).

Postoperative chemoradiotherapy versus post operative radiotherapy alone

The post operative chemoradiotherapy arms in different trials all fared better in terms of better loco regional control and overall survival (53).There was a significant decrease in the rate of distant metastasis in the chemoradiotherapy arm.

Neoadjuvant therapy

Neoadjuvant radiotherapy

The period in which the use of adjuvant therapy was being evaluated also witnessed the adoption of neo adjuvant therapy predominantly in Europe. The rationale for using neo adjuvant radiotherapy was the fact that radiotherapy could provide the possibility of downstaging of tumour leading to better resection with adequate margins or to the possibility of providing a sphincter sparing approach.

The usage of pre operative radiotherapy showed better local control and over all survival rates. The early trials used a short course of hypofractionated radiotherapy followed by surgery after a brief interval. The rates were consistently higher even on a longer follow up (54).

The effect that the interval between the completion of radiotherapy and surgery, had on the oncological outcomes was addressed by another trial that showed that a longer interval allowed for significant downstaging with a higher pathological response rate (55).Pre operative radiotherapy however, led to a higher incidence of complications like bowel urgency, incontinence and fecal soiling.

The drawback of the above trials was the fact that the surgery performed was not the optimal surgical approach as in TME. Preoperative radiotherapy followed by TME compared to TME showed a lower local relapse in the pre operative radiotherapy arm, albeit associated with higher toxicities (56).

The benefit of pre operative radiotherapy with fewer local recurrences with resultant better specific and overall survival was verified by meta analysis (50)

Pre operative chemoradiotherapy versus pre operative radiotherapy

Taking cues from the results of the combined modality arms in the adjuvant setting, the same was attempted in the neo adjuvant setting. The trial showed that the preoperative usage of chemoradiation resulted in higher pathological complete response and lower local relapse rates, but with higher toxicity rates. There was no benefit in terms of overall survival (57) (58).

Overall, preoperative chemoradiotherapy led to fewer local recurrences, higher rates of pathological response compared to radiotherapy alone, while having no effect on disease specific survival or overall survival. There was an increased incidence of grade 3 or more toxicity (59).

The update of the CAO/ARO/AIO-94 trial after a median follow up of 11 years showed the continued benefit of pre operative chemoradiation on local control. There was however no improvement in the overall survival (60). The updated results of another large trial conducted by the EORTC showed a similar benefit from pre operative chemo radiotherapy followed by adjuvant chemotherapy (58) (61).

Neoadjuvant Long Course chemoradiation (LCCRT) followed by surgery and adjuvant chemotherapy is now considered as the standard of care for all locally advanced rectal cancers.

Pre operative short course radiotherapy versus the long course neoadjuvant chemoradiotherapy

The short course radiotherapy regimen (20Gy in 5 fractions) is more popular in Europe whereas the long course neo adjuvant chemoradiotherapy regimen (50.4 Gy in

28 fractions along with 5-FU based chemotherapy) is more popular in the North America. The two were compared in a trial, which showed that though there was a significantly higher rate of pathological response rate and downstaging in the long course regimen, this did not translate into higher rate of sphincter sparing surgery. There was also no significant difference in the rates of toxicity, local recurrence or of overall survival (62). There is no clear 'better' regimen as yet; reports on long-term toxicities are still awaited.

Pre operative versus post operative therapy

Some of the early studies showed only a modest increase in disease free survival with a trend towards increased overall survival in the pre operative chemoradiotherapy arm (63).Some of the later phase III trials showed the benefit of pre operative chemoradiotherapy(50.4Gy in 28 fractions with 5-FU based chemotherapy) in reducing the number of pelvic recurrences, causing significant downstaging and in increasing the number of sphincter sparing surgeries that could be performed. The treatment, however had no advantages when it came to disease free survival or overall survival. It was also noted that there was also lesser acute toxicity in the pre operative arm with better compliance (64) .There was another trial that attempted to evaluate pre operative short course radiotherapy(25 Gy in 5 fractions) versus post operative chemoradiotherapy. It was found that the pre operative arm had lesser number of local failures. There was also an increased disease free survival at 3 years although there was no significant increase in the overall survival (65).

Choice of chemotherapy

Most of the early trials used 5-FU based chemotherapy along with radiation. The low dose continuous infusion of 5-FU was found to be superior to the bolus 5-FU (66).

The other chemotherapeutic agents used in the neoadjuvant setting are:

1) Capecitabine

This is an oral fluoro pyrimidine. It requires the presence of the enzyme thymidine phosphorylase to get converted into the active drug (5-FU) within the tumour cells. The action of Capecitabine closely mimics that of protracted 5-FU infusion. The studies comparing infusional 5-FU versus Capecitabine showed the equivalence of the two drugs with respect to disease free and overall survival. The toxicity profiles were slightly different in that the patients on Capecitabine experienced hand foot skin reactions and proctitis, whereas the patients on infusional 5-FU had myelosuppression (67).

2) Oxaliplatin

The use of Oxaliplatin in combination with Capecitabine or 5-FU has been evaluated. Recent trials have shown that the addition of Oxaliplatin increased the incidence of grade 3 or more toxicity, while not improving the oncological outcomes (68). The addition of Oxaliplatin to a modified 5-FU regimen resulted in higher rates of pathological complete response, the data that looks into the effect of the same on disease free survival is still awaited (69).

3) Irinotecan

Various groups have evaluated the combination of Irinotecan along with infusional 5-FU or with Capecitabine. Though toxicity rates are slightly high, the pathological complete response rate has been in the range of 25-30% (70).The translation of the same into improved oncological outcomes is still awaited.

Locally advanced rectal cancer

Locally advanced rectal tumours are those that are

a) Fixed or adherent to surrounding structures

b) Of a size that is considered inoperable

c) Operable but of a size and character that may not yield adequate margins or have a high probability of leaving behind micro metastatic disease

d)Lymph node positivity

As stated previously pre operative chemoradiotherapy resulted in better local control, cancer specific survival and time to treatment failure. It also had a trend towards better overall survival, although not significant in statistical terms (71).There was an increase in the number of sphincter sparing surgeries that could be performed. One of the few disadvantages of the approach is that these patients experienced marginally more acute toxicity.

In cases where the risk of microscopic residual disease is high, even after chemoradiotherapy, Intra operative radiotherapy may be utilized in an effort to improve the local control. These are still in the experimental phase and require further validation of results and toxicity prior to their routine use (72).

Radiotherapy in rectal cancer

Radiotherapy portals are designed to encompass all possible sites of local recurrences. Recurrences are mainly noted in the pelvic soft tissue, pelvic nodes, anastomotic site or at the perineum (73). Anterior recurrences were mainly noted on in T4 tumours .The lymph nodal groups that are routinely included are the internal iliac as well as the obturator groups. The external iliac group is included only in case of anterior tumour extension or involvement of adjacent structures.

Conventional radiotherapy

Whole pelvic radiotherapy can either be delivered via the commonly used four fields (Box technique) or the 3-field approach (Two lateral and a PA field).

Borders are as follows:

Whole pelvis

AP/PA fields

Superior: Sacral promontory (L5-S1) to encompass the attachment of the posterior peritoneum.

Lateral: 1.5 beyond the widest bony margins of the true pelvis to encompass both the possible lateral extension and the internal iliac chain.

Inferior: 3-3.5cm beyond the lower extent of the tumour. The same can be located either by direct palpation if it is a lower growth, or with the aid of rectal

contrast or an endoscopically placed clip. For post operative cases, in cases of post LAR it is placed 3 cm beyond the region of the anastomosis, or in cases of post April is placed beyond the anal verge to encompass the perineal scar.

The inguinal nodes are encompassed only in case of extension into the anal canal or involvement of the anterior structures.

The para aortic nodes are not included in the portals as the involvement of these is considered to be metastatic disease.

Lateral fields

Anterior: For T2 and T3 leisons-After giving generous margins from the growth it is generally placed at the posterior margin of the pubic symphysis to encompass the internal iliac nodes.

For T4 lesions: Adequate margins from the growth including its anterior extension, it is usually placed at the anterior margin of the pubic symphysis in order to encompass the external iliac nodes.

Posterior: To encompass the entire sacral hollow

Superior and inferior: Margins same as that of AP/PA fields.

The boost field is framed to encompass the primary tumour with a 2 cm margin. The nodes are not routinely included in the boost field.

Manual blocks may be placed to shield the small intestine as well as the soft tissue posterior to the sacrum.

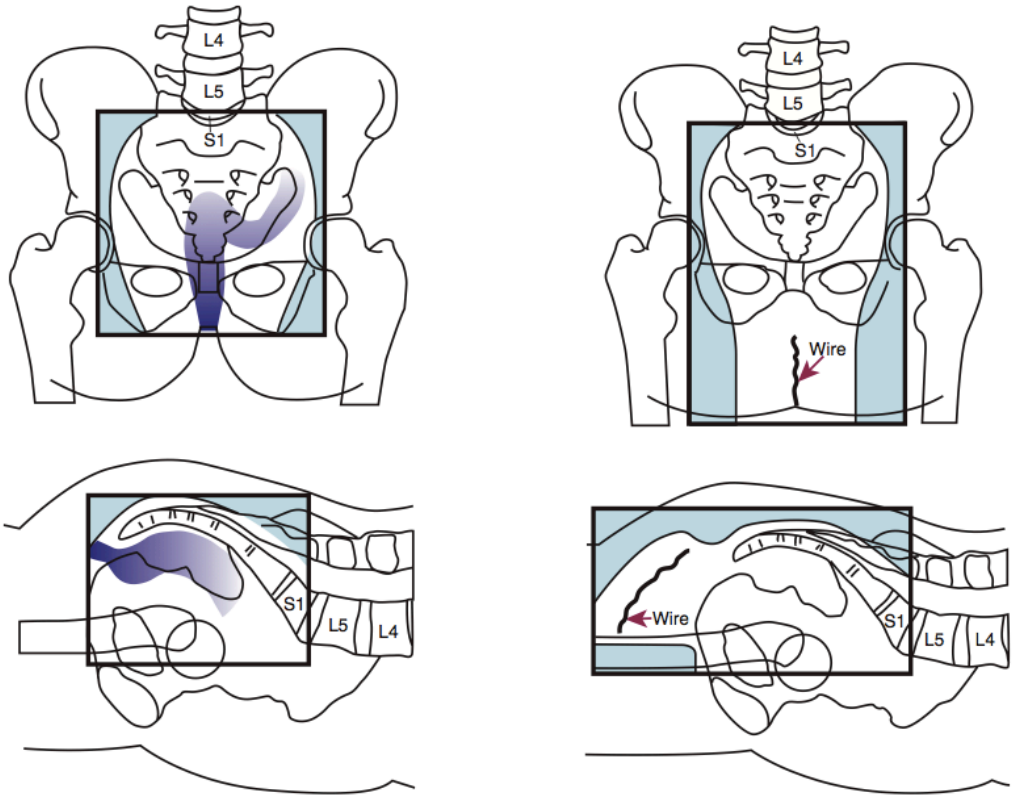


Figure 11: The images on the left are a diagrammatic representation of the portals used post LAR; the images on the right are that of the portals used post APR.

3D conformal radiotherapy

Conformal therapy offers the possibility of sparing normal tissues, while not compromising on the dose delivered to the target volumes.

The GTV includes both the GTV-T and the GTV-N which is appreciated both clinically as well as on imaging.

The CTV includes the entire mesorectum, presacral space as well as the obturator, internal iliac groups. The common iliac and the external iliac are not routinely included in all cases.

The PTV includes a symmetric or asymmetric expansion of the CTV to account for organ motion and set up errors.

The OAR's are routinely contoured and efforts made to limit to spare them well below their threshold limits.

IMRT,though with its potential to reduce normal tissue dose and its resultant advantages, has still not been approved for routine clinical use. Concerns of dose heterogeneity as well as the possibility of geographical miss due to variations in the position of the target has limited the widespread adoption of IMRT in rectal cancer.

Bone marrow

Structure

The bone marrow is one of the largest organ systems in the body contributing to about 5% of the body weight in adults. It is found in the central cavities of long and axial bones. It is the major organ for hemopoiesis, also a primary lymphoid organ, involved in the production of erythrocytes, granulocytes, monocytes, lymphocytes and platelets. It consists of islands of hematopoietic tissue and adipocytes surrounded by vascular sinuses, interspersed within the stromal meshwork of trabecular bone. The hematopoietic tissue consists of blood cells with their precursors, adipocytes, adventitial or barrier cells and macrophages. Hematopoiesis is a compartmentalized process. Erythropoiesis takes place in distinct anatomical units referred to as the 'erythroblastic islands'; granulopoiesis occurs in distinct islands too, albeit, not as organized as the ones involved in erythropoiesis. Megakaryopoiesis, on the other hand, occurs adjacent to the sinus endothelium. The hematopoietic cells reach the bloodstream after entering into the venous sinuses. The platelets, however, are released directly into the blood as cytoplasmic processes of megakaryocytes are in direct relation to the sinus lumen.

Hematopoiesis though a continuous process can be separated into distinct stages. The first stage involves pluripotent stem cells, which are uncommitted stem cells. These stem cells maintain their numbers by a process of self-renewal. They also have the ability to give rise to all hematopoietic cells of any of the above-mentioned lineages. The second stage is when these pluripotent stem cells differentiate into committed stem cells. The committed stem cells may either be of the myeloid or the lymphoid

series (multipotential stem cells). The third stage is when these committed stem cells differentiate into lineage-specific progenitor cells.

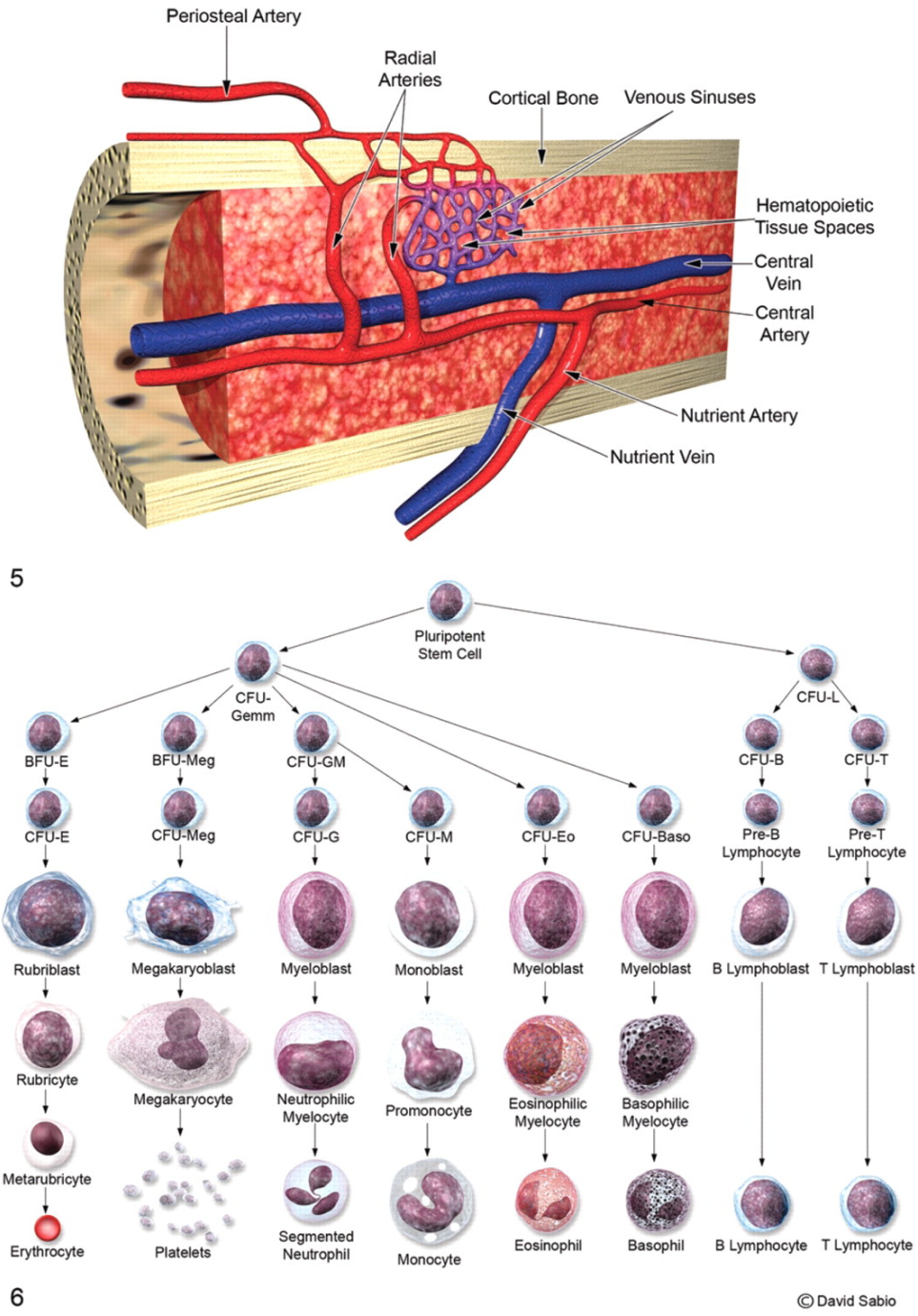


Figure 12: Representation of the marrow with the pluripotent stem cell and the various lineages

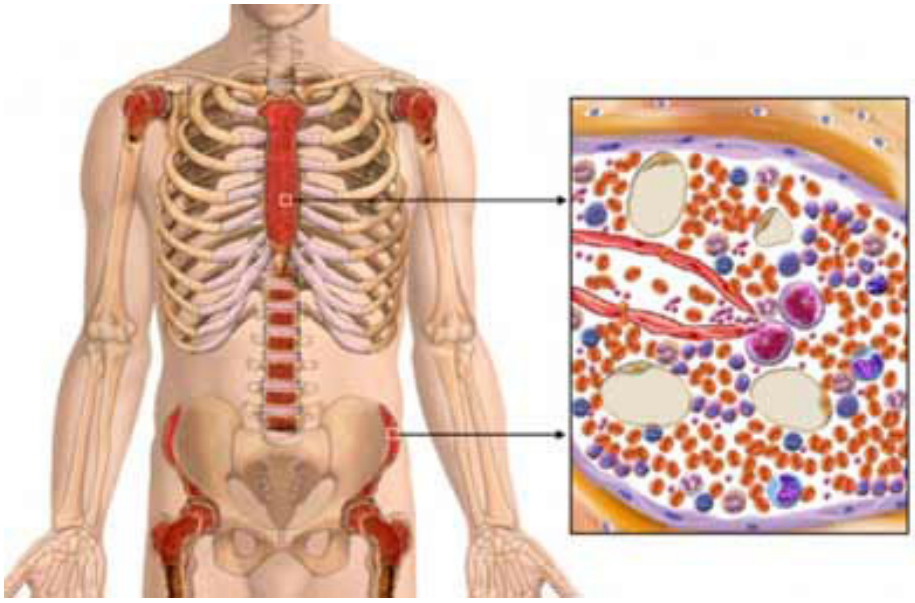


Figure 13: Diagrammatic representation of yellow and red marrow; cellular marrow and adipocytes.

Every step in haemopoiesis; production, differentiation and maturation is under the regulation of humoral factors. The humoral factors may either be general or be specific for particular lineages. They may also be specific for either the early non-committed cells higher up in the production process or to the more committed lineage specific progenitor cells.

The distribution of active marrow in human adults is considerably different from those in children. About 40% of the marrow is located in the pelvis, 10.9% in the lumbar spine, 14.1% in the thoracic spine, 13.1% in the calvaria, 8.3% in the upper limb girdle and the remaining in the ribs, cervical spine and the sternum.

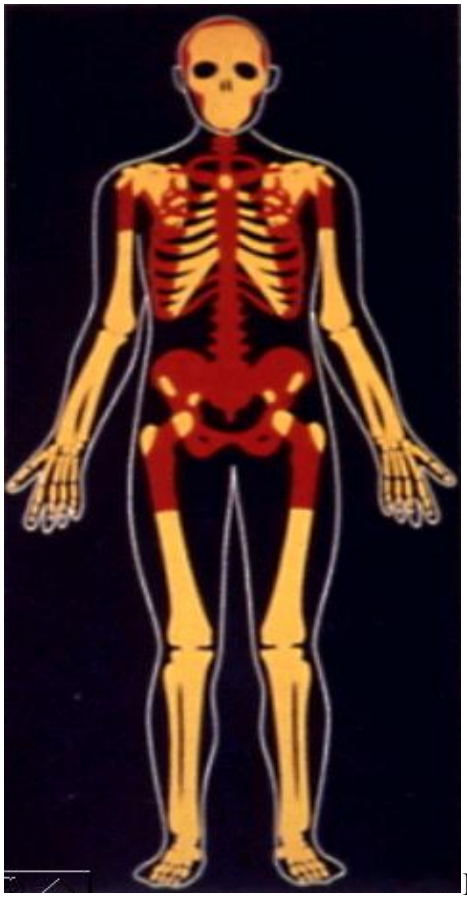


Figure 14: Distribution of red marrow in adults

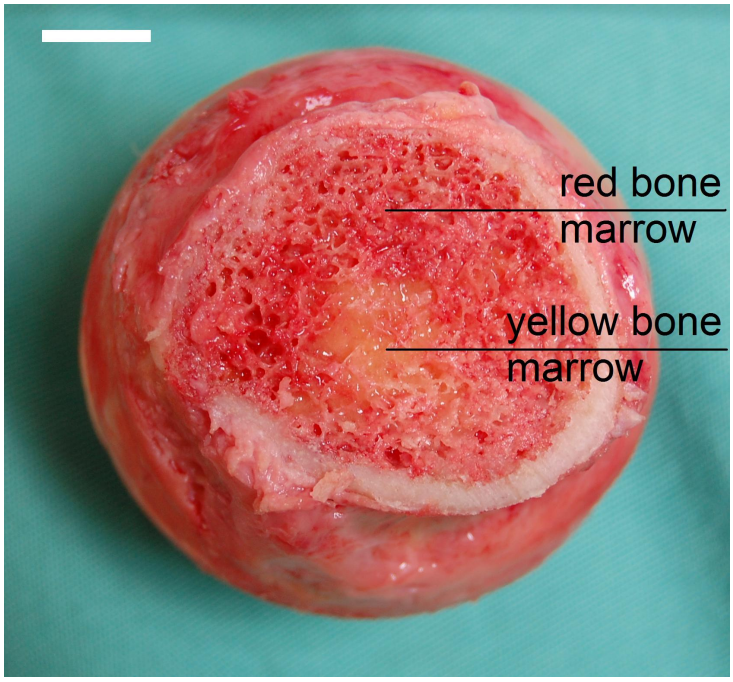


Figure 15: Gross visualization of red and yellow marrow

Percentage of total bone marrow activity by bony site

Site	Mean ± SD
Skull	2.9 ± 2.1
Proximal humeri	1.9 ± 1.2
Sternum	2.9 ± 1.3
Ribs and clavicles	8.8 ± 4.7
Scapulas	3.8 ± 0.9
Cervical spine	4.3 ± 1.6
Thoracic spine	19.9 ± 2.6
Lumbar spine	16.6 ± 2.2
Sacrum	9.2 ± 2.3
Pelvis	25.3 ± 4.9
Proximal femurs	4.5 ± 2.5

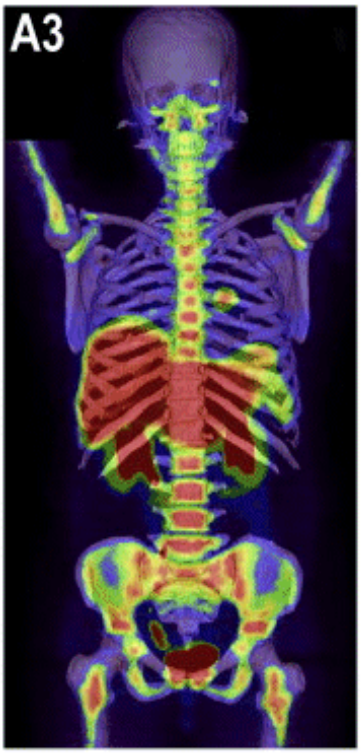


Figure 16: Distribution of active marrow in adults with corresponding site-specific percentages

The fact that the cellularity of the bone marrow varies with age is well known. The bone marrow of children is more cellular than that in adults. The cellularity is usually expressed as the ratio of nucleated hematopoietic cells to fat cells. The ratio is about 70:30 in young adults, where as in the elderly it usually drops to 30:70.

Effect of radiation on bone marrow

The bone marrow is exquisitely sensitive to radiation. The bone marrow is one of the organs that have been exhaustively studies by radiobiologists. The effects of radiation on the bone marrow were described soon after the discovery of X rays. The mechanisms or bone marrow destruction and the clinical implications of the same were described in more detail while investigating the clinicopathological features of acute radiation syndromes. The difference in kinetics and turnover of cells of different lineages are reflected in the clinical and pathological features that are noticed following radiation exposure. The same is also responsible for the differences noted in attaining normal state kinetics in the period of recovery.

The peripheral blood picture of granulocytopenia, thrombocytopenia and anemia partly reflect the early effects of the damage caused by radiation. The do not give an indication of the extent of damage to the microenvironment, the reserve capacity of the marrow or to the damage caused to the stem cells.

The pluripotent stem cells and blast cells are more radiosensitive than the mature post mitotic cells. In both murine as well as in human models the most primitive stem cells appear to be responsible for long-term hematopoiesis. The committed stem cells aid in engraftment and the initial hematopoietic recovery. Invitro assays or explanted stromal cells have been used to study radiation-induced injury to the microenvironment.

The hematopoietic syndrome that occurs after a whole body exposure of 2.5-10 Gy is predominantly due to neutropenia and thrombocytopenia. In fractionated

doses, however, even large fields upto 20-40 Gy can be tolerated with minimum residual effects. This is probably due to the capacity of stem cells from the nonirradiated marrow and peripheral blood to seed into the bone that has been irradiated. The process of recovery follows a characteristic pattern wherein the platelets and granulocytes return to their normal values before the erythrocytes do. Complete recovery of hematopoiesis is however seldom possible due to the irreversible stromal and microvasculature injury. Reduced production of humoral factors may also be a contributory cause.

The delayed effects of localized exposure, in addition to the dose, volume of marrow irradiated and fractionation, also depends on age. Children appear to have a greater capacity for marrow recovery than adults (74).

Imaging of the bone marrow

1) Plain radiographs and Computed tomography: Though information about the structure of the bone is obtained, visualization of the bone marrow is not possible.

2) Nuclear medicine imaging: Functional imaging using the above pharmaceuticals, along with their appropriate targets, holds great promise in imaging of the functional marrow. The common drawback is however, the poor spatial resolution with the resultant lack of structural information (75).

Radiopharmaceutical	Physical half life	Effective dose to bone marrow per MBq (mSv)	Cyclotron	Quantification (absolute)	Target
Gamma camera					
^{99m}Tc-sulphur colloid	6 h	0.0019	–	–	RES
^{99m}Tc-nanocolloid	6 h	0.0094	–	–	RES
^{111}In-chloride	2.3 days	0.21	–	–	Erythropoietic
^{99m}Tc-WBC	6 h	0.023	–	–	RES
^{111}In-WBC	2.3 days	0.36	–	–	RES
^{99m}Tc-AGAb	6 h	0.0055	–	–	Granulopoietic
PET					
^{52}Fe	8.2 days	6.1	+/–	+	Erythropoietic
^{18}F-FDG	2 h	0.011	+/–	+	Metabolic activity (glucose)
^{18}F-FLT	2 h	0.029	+/–	+	Proliferative activity (DNA)
^{11}C-methionine	20 min	0.00045	+	+	Metabolic activity (amino acid)
^{11}C-acetate	20 min	0.0057	+	+	Metabolic activity (fatty acid)
^{11}C-choline	20 min	0.0019	+	+	Cell proliferation
^{18}F-choline	2 h	0.012	+/–	+	

Figure 17: Radiopharmaceuticals used in functional imaging of bone marrow

3) Magnetic resonance imaging: Of the limited radiological options available, MRI is the preferred modality for visualization of the marrow. Trabecular bone, water and fat all have different MR signals. The relative contributions of the above three along with their summated MR signals is responsible for the final MR image. The predictable rate and patterns of red to yellow marrow conversion and their corresponding characteristic features of the MRI have allowed the mapping of the bone marrow varying with age. The adult red and yellow marrow distribution is generally reached by the age of 20 (76).

The standard MR imaging protocol for visualization of the bone marrow may include coronal STIR images of the spine, pelvis and sagittal T1-w and fat-suppressed, T2-w FSE or STIR sagittal images of the spine. Axial and contrast-enhanced T1-w images are acquired in when appropriate(76)

T1-w images:

- Yellow marrow has a bright signal similar to that of subcutaneous fat
- Water appears hypo intense
- The red marrow with 40% water, 40% fat and 20% protein appears darker than yellow marrow, with signal intensity slightly more than that of muscle.

T2-w images:

- Yellow marrow appears hypointense
- Water appears bright
- The resultant image of the red marrow appears relatively unchanged, appears slightly more intense than the muscle.
- T2w-SPE with selective fat suppression offers a little more distinction between the yellow and the red marrow than a conventional T2-w image

STIR:

- Short inversion –Time inversion recovery with the advantage of eliminating signal from a selective tissue helps in visualization of the pathological area against a backdrop of the uninvolved marrow. Coronal STIR images with a large field of view helps in volumetric assessment a large area.

Contrast enhanced T1-w images:

- Useful when findings are not discernable on an unenhanced T1-w series.
- Appropriate when diffuse marrow or meningeal involvement is expected

Imaging findings post radiotherapy

The changes observed post radiotherapy result in an increased T1-w signal with a sharp demarcation corresponding to the radiation portal.

The sinusoidal vasculature is affected post radiotherapy; the hematopoietic marrow is replaced by the fatty marrow with the resultant hypocellular bone marrow. There have been reports that at doses above 36 Gy, fatty replacement is permanent, with little chance of hematopoietic recovery. Below 30 Gy, however, these changes are likely to be reversible in 12–24 months (77) (78) .

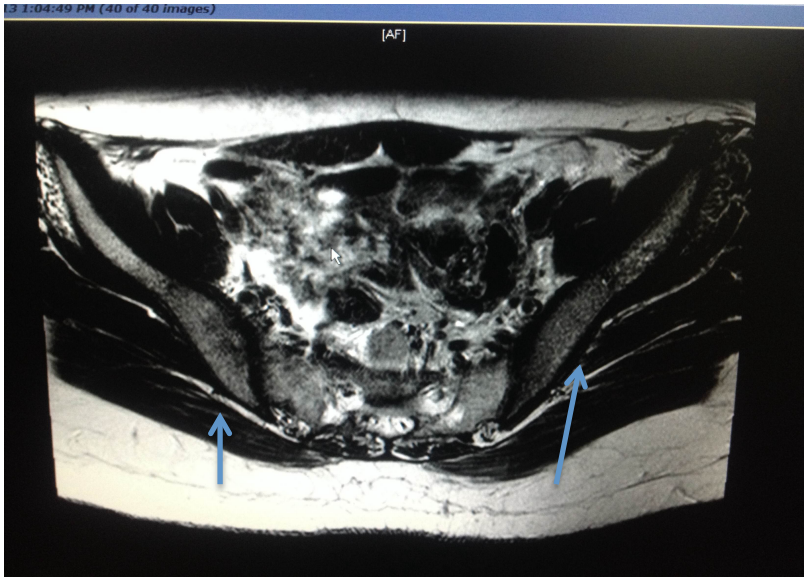


Figure 18: T1-w images of the pelvis in coronal section (Pre Neoadjuvant chemoradiotherapy) Note the hypointense areas representing the areas of red marrow (indicated by arrows)

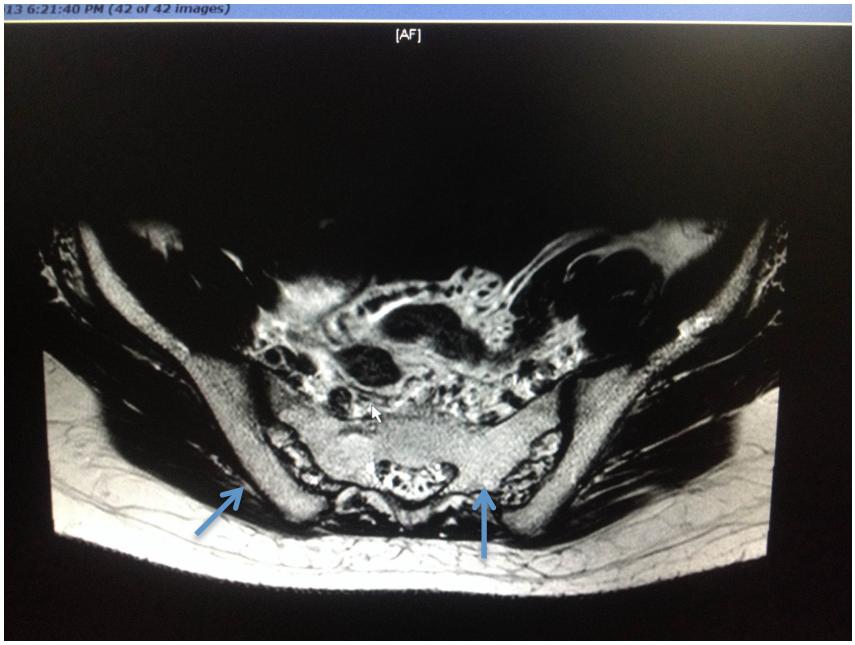


Figure 19: T1-w image of the pelvis in coronal section (Post Neoadjuvant chemoradiotherapy); Note the hyperintensity in the sacrum and iliac crests indicating the presence of yellow marrow; indicated by arrows.

Implications of bone marrow depletion

Approximately 51% of the active marrow is located in the lumbosacral spine along with the pelvic girdle. This is of particular interest to the radiation oncologist, as radiotherapy for the treatment of lower gastrointestinal, gyneaecological or prostatic malignancies involves fields that would encompass the above mentioned areas.

It is well known that both radiotherapy and chemotherapy have considerable effects on the bone marrow in causing myelosuppression. The effects are of an even greater significance in cases of radiotherapy along with concurrent chemotherapy, in which case there is an additive effect of the individual bone marrow toxicities from radiotherapy and chemotherapy. The resultant toxicity noticed during the course or following completion of chemoradiotherapy is by no means insignificant.

It may lead to the following:

a) Degrees of hematological toxicity, which would warrant interrupting therapy.

b) Febrile or afebrile neutropenic illnesses with its associated morbidty, risk of mortality and their associated cost of management.

c) Need for supportive medications including blood product support

d) Persistent neutropenia leading to discontinuation of further therapy

e) Depletion of marrow reserves to an extent, which could compromise future adjuvant therapy.

Of considerable concern in the management of lower gastrointestinal and gynaecological malignancies is when the use of radiotherapy involving large pelvic fields along with concurrent chemotherapy, has the potential to cause significant acute and sub acute hematological toxicity. Peripheral blood investigations done during the course and following completion of therapy reflect only the acute changes observed. It does not, however, estimate the degree of damage caused to the marrow or its reserve. Bone marrow biopsies are also unable to characterize the above changes fully. Due to the paucity of methods to characterize or visualize the damage to the bone marrow, efforts to reduce the dose the bone marrow were seldom made in the past.

Initial efforts to reduce the dose to the active bone marrow involved using 4 field box techniques, placing manual shields to spare the ilium and the iliac crests. With the advent of conformal and intensity modulated radiotherapy techniques, multiple beams were placed along with appropriate shielding offered by customized blocks, and multi leaf collimators resulting in significantly reduced doses to the organs at risk (OAR's). Further efforts involved the contouring of the entire pelvis on the planning CT and limiting the dose to the OAR's including the pelvis without compromising the dose delivered to the target volumes. "Bone marrow sparing IMRT" has been recently attempted both prospectively in the clinic as well as in dosimetric studies in the treatment of gynaecological malignancies as well as in anal cancers(4)(79)(80)(81)(82)(83). The studies showed significantly lesser doses

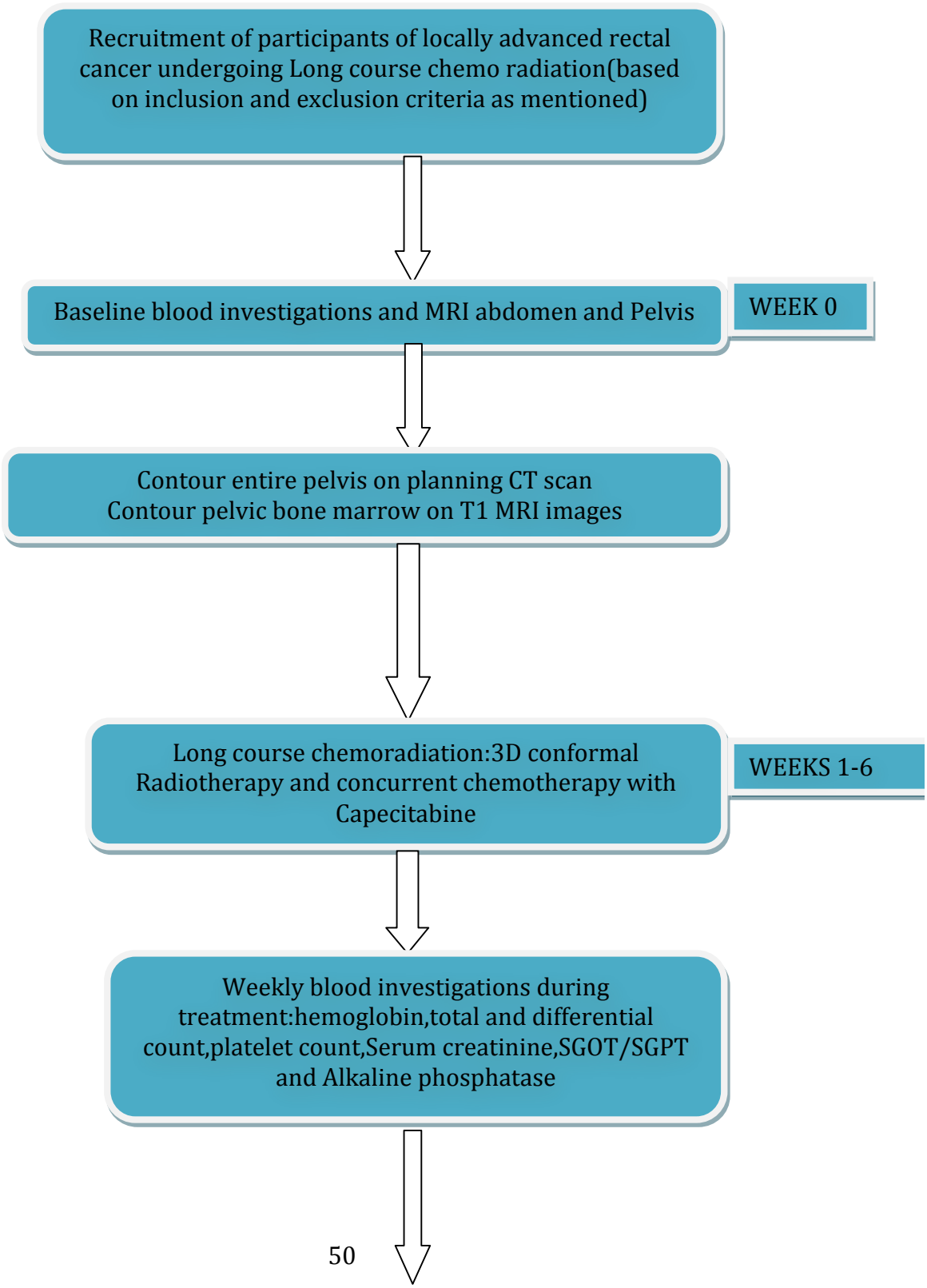
received by the pelvis. This translated into lesser hematological toxicities, lesser number of emergency visits and lesser treatment breaks(84)(85)(86)(87).This however resulted in gross over estimation of the amount of active marrow(88)(84).

With the developments of novel imaging modalities such as the FLT PET, FDG PET, SPECT and the MRI (T1 sequences, DCE) efforts are now being made to contour the active marrow alone such that more accurate estimates of the volume and their tolerance may be obtained (89)(90). The above methods are however, still in the experimental phase and not yet being used in routine clinical practice.

Materials and methods

Study *design*

Algorithm of study



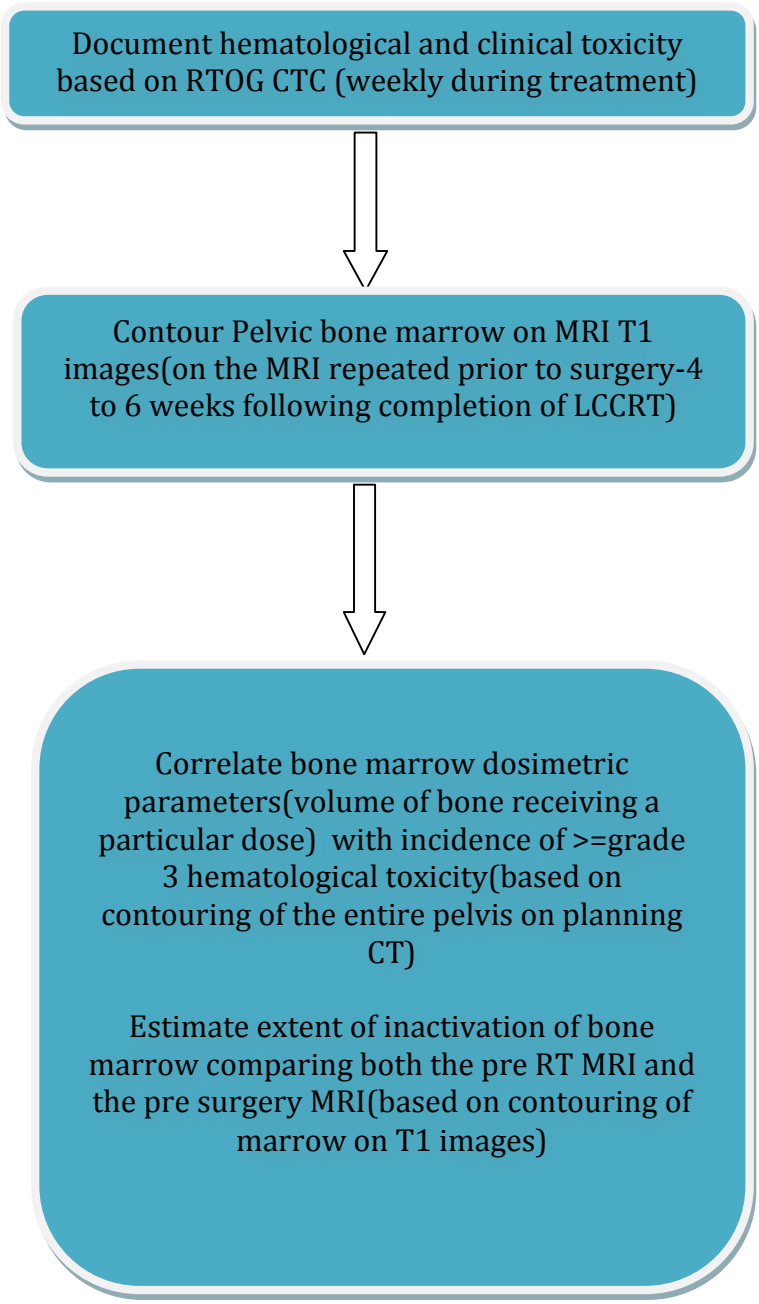


Figure 20: Algorithm indicating the study design

For the study it was decided to recruit participants from the departments of Radiation oncology (Unit-I) and surgery (Surgery-II) from Christian Medical college, Vellore.

A search from our departmental unit database was carried out for all patients with rectal cancer who had undergone 3D conformal radiotherapy.

From the above broad search, participants were recruited based on the fulfilment of inclusion criteria.

Inclusion criteria

- Locally advanced rectal cancer: clinical or radiological evidence of T3/T4 or N1 evidence; or that is and/or clinically bulky
- No evidence of distant metastasis
- Adenocarcinoma
- Considered or being considered for neo adjuvant Long course radiotherapy (3D conformal RT) along with concurrent chemotherapy (concurrent Capecitabine)/or completed treatment as previously mentioned
- Underwent pre and post RT MRI in our Institution

Exclusion Criteria

- History of prior pelvic malignancies
- History of prior radiation to the abdomen/pelvis
- Prior history of usage of chemotherapy/immunosuppressant
- Known case of myelodysplastic syndrome/myelofibrosis
- Participants with outside MRI films (either pre radiotherapy or post radiotherapy/pre surgery MRI) were not considered for the study (unless the same were repeated at our hospital).

Sample size estimation

The sample size for the study was determined after discussion with the statistician.

It was determined as follows:

Sample size for comparing toxicity rates:

$N=(Z\ (1-a/2)+Z1-b))^2.\ P_1(1-P_1).P_2(1-P_2)\ /\ (P_1-P_2)^2$

5% level of significance Z (1-a/2)=1.96

80%Power = Z1-b= 0.84

$D=(P_1-P_2)^2$=Difference in the toxicity rate

A sample of size of 26(13 receiving less than the threshold dose and an equal number receiving more than the same specified threshold) was needed to detect the difference of 60% toxicity level between the groups with 80% power and 5% level of significance using an uncorrected chi-square test

IRB clearance

Clearance from the institutional review board and ethical committee was obtained on May 08,2014

The prospective patients were recruited into the study after taking their informed consent (Enclosures 1-4)

However, due to unforeseen slow accrual of patients we sought the permission of the IRB to modify the study design so that we could recruit retrospective patients as a part of the study .The same was approved by the committee on July 24,2014.

Work-up

All patients had undergone a complete staging as well as a metastatic work up. A baseline CBC including Haemoglobin, total count, differential count, platelet count, renal and liver function tests, CEA, ECG, Echocardiograph, Chest radiograph, MRI of the abdomen and pelvis was obtained for all patients. Height,Weight,baseline BSA was calculated for all patients. Cardiology clearance was taken prior to starting chemotherapy.

Other parameters that were recorded were:

Location of the tumour (upper, middle or lower rectum)

Proliferative or ulcerative tumour

Presence or absence of circumferential involvement

Presence or absence of anorectal involvement.

Staging of rectal cancer was based AJCC cancer staging manual 7th edition, 2010

The clinical and radiological findings of all patients were discussed in a multi disciplinary tumour board comprising of Radiation Oncologists, Surgical Oncologists, Medical Oncologists, Diagnostic and Radiologists .The consensus decision was to offer Neoadjuvant radiotherapy using 3D conformal radiotherapy along with concurrent chemotherapy with daily Capecitabine.

All the patients in this study were proposed to receive neo adjuvant long course chemoradiotherapy using 3D conformal technique.

3D Conformal therapy

Position:

All patients were simulated and treated in the supine position. The forearms and hands were placed over the chest or upper abdomen, based on the patient's preference

Immobilization:

An immobilization device utilizing a vacuum assisted bag the VAC-LOC was made for all patients.

3 Fiducial markers were placed on the patient's body and their positions prior to CT simulation were verified by aligning them using the in-room lasers.

Planning CT protocol

The simulation CT was acquired as follows:

Informed consents for using oral and IV contrast were taken.

Patients were asked to lie supine on the flat couch insert along with the vacloc and the positions of the patient and the fiducials were verified.

Oral contrast was given to aid in visualization of the small bowel.

IV cannulas were placed and their patency verified.

The scout film was viewed to verify patient position.

IV contrast (1ml/Kg) was injected using a machine driven piston.

5mm cuts were acquired from the level of the diaphragm superiorly to the level of the mid thighs inferiorly.

Target delineation

Volume delineation was carried out as follows:

GTV: The rectal growth visualized on imaging. Clinically or radiologically involved nodes.

CTV: Areas of subclinical disease extension including the entire mesorectum, presacral space and the internal iliac group of lymph nodes.

PTV: Symmetric or asymmetric expansion of the CTV to account for set up and systematic errors.

*Phase **I***: The above-mentioned PTV

Phase II: The tumour or the post operative site with a 3 cm margin. The nodal stations were not routinely included in the phase II volume.

Protocol for contouring of the entire pelvis on planning CT

The entire pelvis and parts of the lumbosacral spine and proximal femurs including the head and trochanters were contoured on the planning CT for all patients.

Contouring was carried out as follows:

The bone window was used.

Entirety of the bone from L5-S1 junction or from the level of the superior most section including the PTV phase I, whichever was higher. The inferior extent was at the lowermost level of the ischial tuberosity.

The dosimetric parameters relating the bone marrow such as V5, V10, V20, V30 and V40 were recorded.

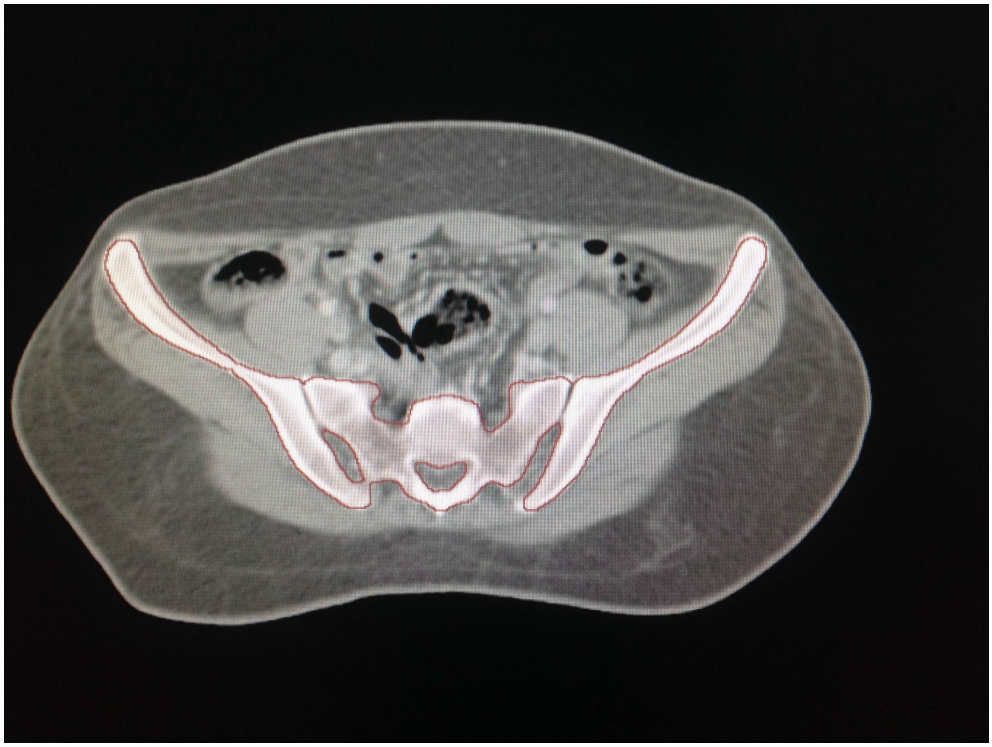


Figure 21: Delineation of the Pelvis on the planning CT

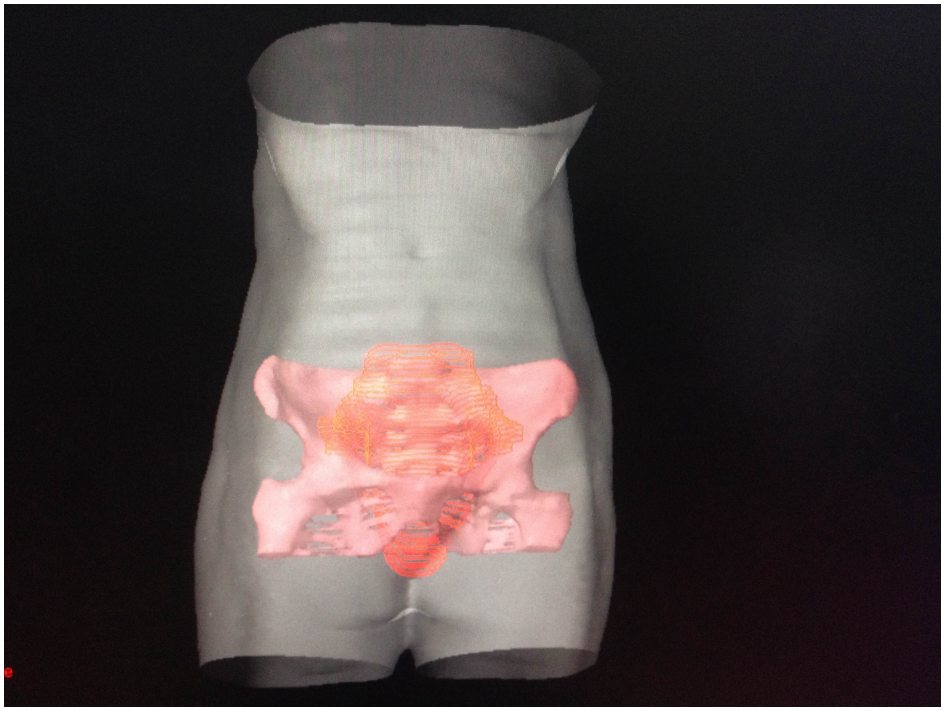


Figure 22: 3-D reconstruction of the delineated pelvis (pink) and the PTV (Red)

Protocol for estimating marrow inactivation

The active marrow (red marrow) was contoured on the MRI abdomen and pelvis on the T1 weighted images along with the assistance of a senior radiologist.

The images that were acquired were reviewed by the radiologist. The active marrow on both the pre radiotherapy MRI as well as the post radiotherapy MRI was contoured by the radiologist as follows:

The yellow marrow has hyperintense signal intensity on T1; red marrow has a relative hypointense signal intensity compared to yellow marrow but a higher intensity than that of the muscle.

The marrow was delineated on the axial images; the superior and inferior limits being the same as that used for contouring the bone on the planning CT. The summated volumes of the active marrow on both the pre as well as the post treatment MRI's were recorded. The percentage inactivation of active marrow was also calculated.

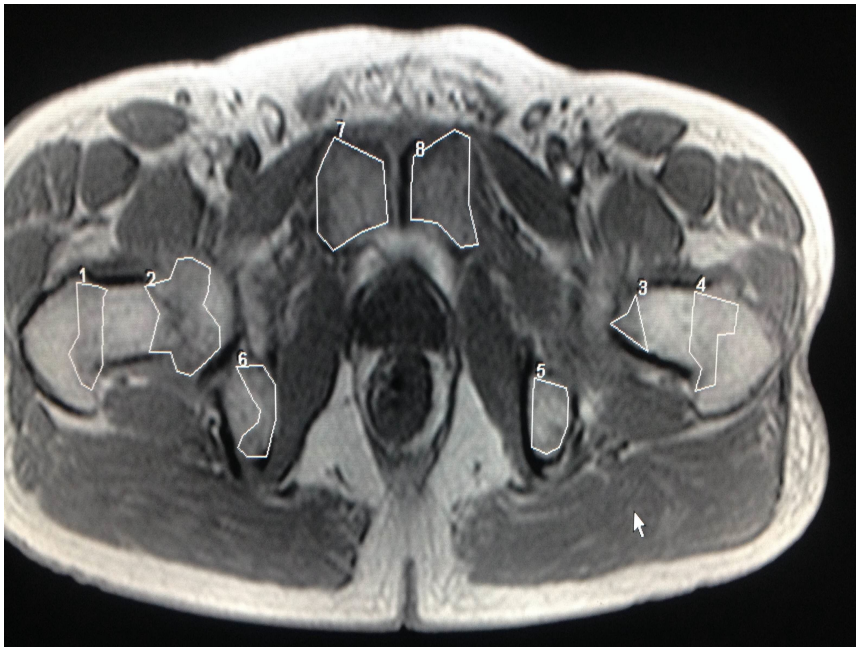


Figure 23: T1-w axial images of the pelvis. The hypointense areas were contoured indicating islands of active marrow (areas numbered 1-8).

Figure 24: Hypointense areas on T1-w axial images representing islands of active red marrow (areas numbered 1-8;denoted by blue arrows

Plan evaluation

The plans were evaluated based on ICRU principles where in the target volume coverage and distributions were reviewed while ensuring that the organs at risk received a dose that was within their tolerance limits.

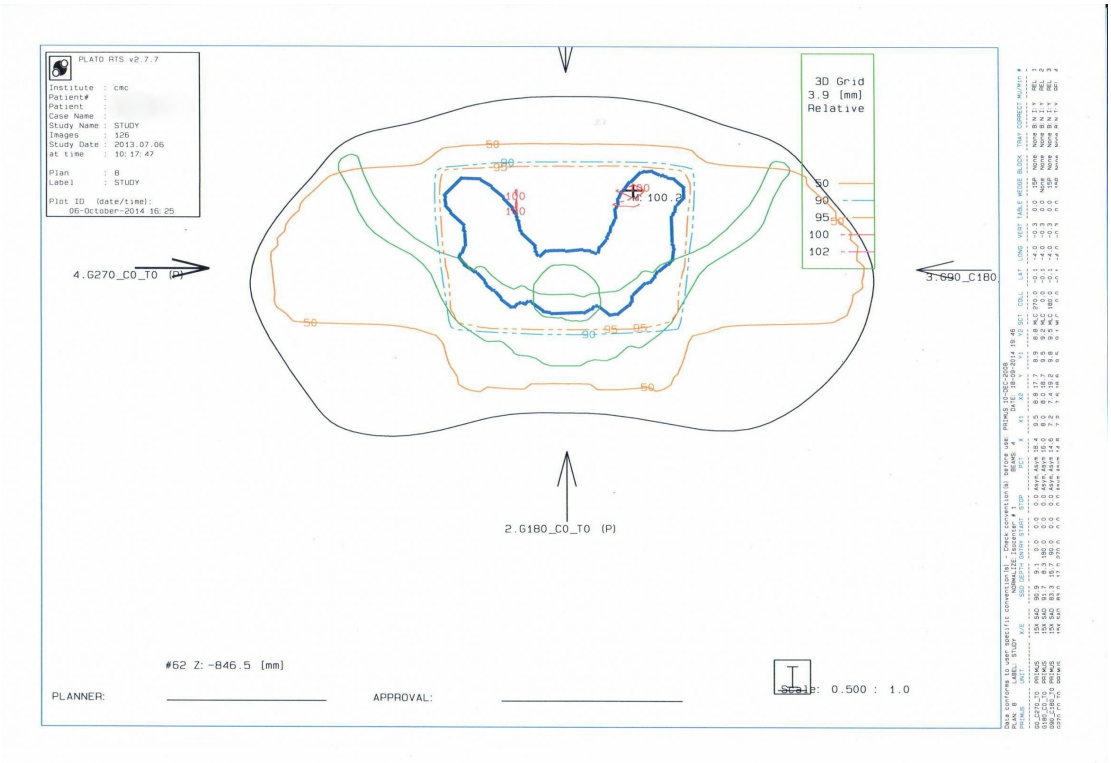


Figure 25: Isodose coverage of the targets as a part of plan evaluation

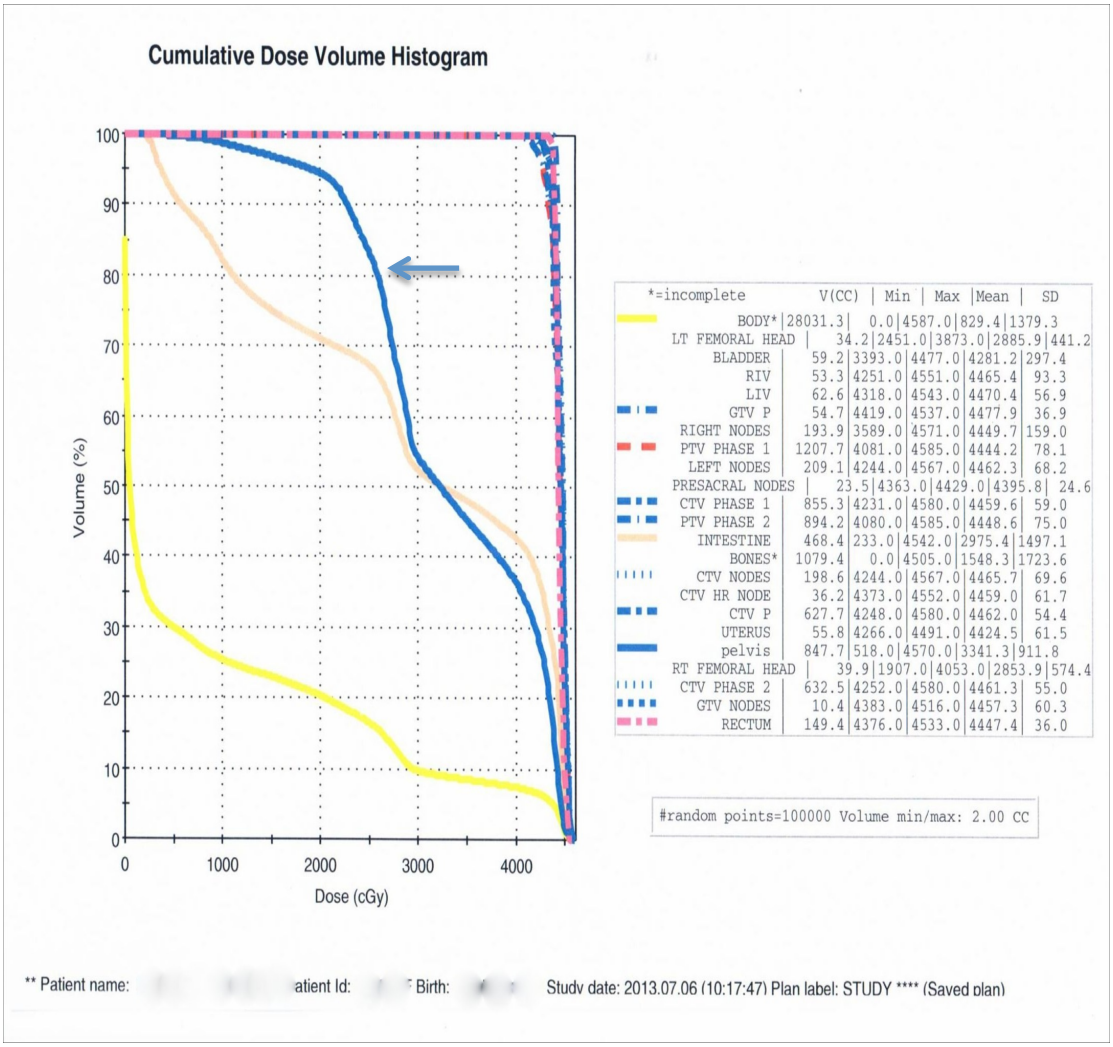


Figure 26: DVH of both the target volumes as well as the organs at risk; note the blue unbroken line representing the DVH of the pelvis (represented by the arrow)

Treatment delivery

All patients received treatment on the SIEMENS PRIMUS linear accelerator with a dose of 45Gy in 25 fractions delivered to the phase I volume followed by an additional 5.4Gy in 3 fractions delivered to the Phase II volume.

Concurrent chemotherapy

All patients received concurrent chemotherapy with Capecitabine (825mg/m2) given Monday to Friday (on the days of receiving radiotherapy)

The need, the benefits and side effects expected with radiotherapy and chemotherapy were explained to patients and their informed consents taken.

Weekly assessment

Patients underwent a weekly assessment during the course of radiotherapy. Clinical toxicities were documented as per the RTOG toxicity grading system. Weekly blood investigations including Hemoglobin, total and differential counts, platelet count, liver function tests and Serum creatinine were ordered.

Patients underwent a reassessment of their disease status 6 weeks following completion of the Neoadjuvant treatment. Apart from the above-mentioned investigations, they also underwent MRI of the pelvis to assess tumour downstaging.

Variables

The variables that were considered were:

1) Hematological toxicities-

Toxicities relating to Hemoglobin, Total leucocyte count, absolute neutrophil count, lymphocyte count and platelet count were graded separately according to the Cooperative group common toxicity criteria (RTOG)

2) Bone Dosimetric parameters-

Such as V5, V10, V20, V30 and V40 both in terms of absolute volume in cc as well as the relative volume in percentage.

3) Volume of active marrow-

The volumes on the pre radiotherapy MRI, the volume of active marrow noted on the post radiotherapy MRI and the percentage inactivation of active marrow were noted.

Sources of Data

The source of data was as follows:

Clinical data- Department of Radiation oncology

Radiological investigations-MRI Pelvis and abdomen (Pre and Post radiotherapy-baseline and the MRI repeated 4-6 weeks after LCCRT)-Department of radiodiagnosis

Histopathology-Department of pathology

Hematological investigations: Hemoglobin, Total count, Differential count, Platelet count-Department of Clinical pathology

Biochemical profile: Liver function tests, Serum creatinine, Serum urea, Serum Electrolytes-Department of Clinical Biochemistry

Dose of Radiation delivered to the bone marrow-Generation and Interpretation of the DVH on the TPS-Departments of Radiation Physics and Radiation Oncology.

The incidence of haematological toxicity, the grade of toxicity and its correlation with the bone dosimetric parameters were attempted.

The incidence and grade of haematological toxicity and its correlation with the percentage inactivation of the active marrow was also carried out.

	TOXICITY	- 0 -	- 1 -	- 2 -	- 3 -	- 4 -
Blood/Bone Marrow	WBC	>=4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
	Platelets	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	<25.0
	Hemoglobin	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	<6.5
	Granulocytes/Bands	>=2.0	1.5 - 1.9	1.0 - 1.2	0.5 - 0.9	<0.5
	Lymphocytes	>=2.0	1.5 - 1.9	1.0 - 1.2	0.5 - 0.9	<0.5

Figure 27: RTOG toxicity criteria

Statistical methods

The statistical methods were carried out as follows:

The data was summarized using weekly blood counts, weekly toxicities of Haemoglobin, Leucopenia, Neutropenia, Lymphopenia, Thrombocytopenia, the lowest toxicity graded during the course of chemoradiotherapy. The absolute volumes as well as the percentages of the bone marrow were recorded in each of the dosimetric groups (V5, V10, V20, V30 and V40).

The Volumes of the marrow seen on the pre radiotherapy MRI as well as on the post Radiotherapy MRI were recorded both in absolute volume in cc as well as in percentages.

Univariate analysis of each of the dosimetric groups was carried out. The mean, the standard deviation, the median and the quartiles were tabulated.

The correlation between the toxicity levels (grade 3 and more) and the bone dosimetric variables were compared using the Shapiro Wilk test and the Mann Whitney test (Two sample Wilcoxon rank sum test).

A paired T-test was applied to find out the difference between the pre and the post chemoradiotherapy bone marrow volumes.

Results

We carried out a search of our departmental unit database (Department of Radiation Oncology-Unit I), for patients with locally advanced rectal cancer who received 3D conformal radiotherapy.

From January 2012 to August 2014,we identified 27 patients who met the above two criteria. On reviewing the clinical and treatment details, we found that 7 patients were not suitable for the study as they did not meet the eligibility criteria. The biopsies of the rectal growth of two of the seven patients were not reported as adenocarcinoma (being neuroendocrine tumour in one and melanoma in the other). 3 patients out of the above seven had undergone upfront surgery and received radiotherapy as adjuvant therapy.

3 patients out of seven had received chemotherapy prior to initiation of radiotherapy.6 patients had received neo adjuvant chemoradiation using 3D conformal therapy, but had to be excluded from the study as they did not have the post radiotherapy MRI of the pelvis.

After excluding the above patients we analyzed the details of 20 patients who met the eligibility criteria.

Patient Demography

ID NO	AGE	SEX	MARITAL STATUS	OCCUPATION
1	41	Female	Married	Skilled worker
2	55	Male	Married	Skilled worker
3	44	Male	Married	Skilled worker
4	52	Female	Married	Skilled worker
5	65	Male	Married	Skilled worker
6	56	Male	Married	Skilled worker
7	64	Female	Married	Skilled worker
8	29	Male	Umarried	Skilled worker
9	57	Male	Married	Skilled worker
10	36	Female	Married	Skilled worker
11	67	Female	Married	Skilled worker
12	64	Male	Married	Skilled worker
13	66	Male	Married	Skilled worker
14	69	Male	Married	Skilled worker
15	53	Female	Married	Skilled worker
16	64	Female	Married	Unskilled worker
17	41	Male	Married	Skilled worker
18	57	Male	Married	Skilled worker
19	53	Female	Married	Skilled worker
20	19	Female	Unmarried	Unskilled worker

Table 1: Demographic details

AGE	NUMBER	PERCENTAGE
<45 yrs	6	30
>45 yrs	14	70

Table 2: Table with representation of patients less than 45 years of age

We found that there were 11 male and 9 female patients with a mean age of 52 years (range 19-69). 30% of the patients were below the age of 45 years.18 patients were married and 2 were unmarried.

Tumour characteristics

Id No	Location Of Tumour	Anorectal Involvement	Circumferential Involvement
1	Lower	Yes	Yes
2	Lower	Yes	Yes
3	Upper	No	No
4	Lower	No	Yes
5	Middle	No	Yes
6	Middle	No	Yes
7	Upper	No	Yes
8	Middle	No	No
9	Lower	Yes	No
10	Middle	No	No
11	Lower	Yes	Yes
12	Middle	No	Yes
13	Upper	No	Yes
14	Upper	No	Yes
15	Upper	No	No
16	Lower	Yes	Yes
17	Lower	Yes	Yes
18	Upper	No	Yes
19	Upper	No	No
20	Upper	Yes	Yes

Table 3: Table with tumour characteristics

8 patients had upper rectal growths, 5 in the middle rectum and 7 in the lower rectum.7 patients had involvement of the anorectum. It was also noted that 14 patients had a circumferential growth.

Stage characteristics

T Stage

T STAGE	NUMBER	PERCENTAGE
2	0	0
3	15	75
4	5	25

Table 4: T stage characteristics

Nodal involvement

NODAL STAGE	NUMBER	PERCENTAGE
0	1	5
1	6	30
2	13	65

Table 5: N stage characteristics

Since only patients with locally advanced rectal cancer were considered, 15 patients had T3 disease whereas 5 patients had a T4 growth. 12 patients had an N2 status, while 5 had a nodal status of 1.There was only one patient who had no radiologically detected nodes. No patients with metastasis were included in the study. All patients had a performance score of either 0 or 1.

Dosimetric variables

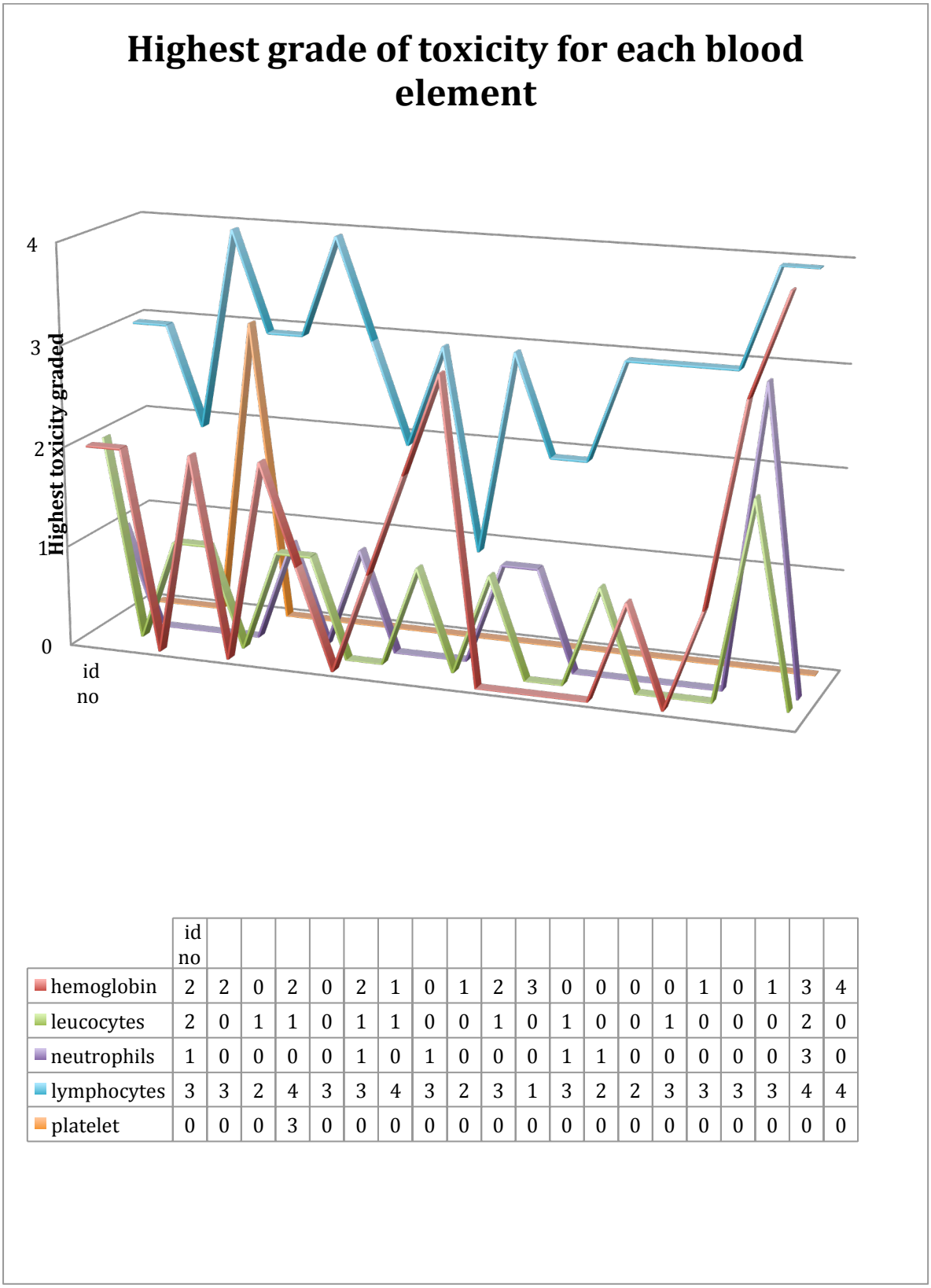
Univariate analysis of the bone dosimetric variables were as follows:

1) *V5*: The median value of V5 was 99.83%(959.07cc) ranging between a minimum and maximum values of 88.75%(631.94cc) to 99.99%(1430.63cc)
2) *V10*: The median value of 97.62%(931.32cc) ranging between 82.88%(629.97cc) to 99.99%(1403.83cc)
3) *V20*: The median value of 93.91%(872.98cc) ranging between 65.14%(615.38cc) to 98.97%(1361.69cc)
4) *V30*: The median value of 66.27%(618.26cc) ranging between 50%(310.04cc) to 93.54%(880.21cc)
5) *V40*: The median value of 45.50%(444.40cc) ranging between 36.58%(300.74cc) to 56.25%(635.61cc)

Toxicity grading

Weekly blood investigations were recorded and the grading of toxicity for different blood elements was carried out on a weekly basis. In addition to the weekly grading of toxicity, the highest grade of toxicity experienced during the course of neo adjuvant chemoradiotherapy was also noted.

Results were as follows:



	id no																		
hemoglobin	2	2	0	2	0	2	1	0	1	2	3	0	0	0	0	1	0	1	3	4
leucocytes	2	0	1	1	0	1	1	0	0	1	0	1	0	0	1	0	0	0	2	0
neutrophils	1	0	0	0	0	1	0	1	0	0	0	1	1	0	0	0	0	0	3	0
lymphocytes	3	3	2	4	3	3	4	3	2	3	1	3	2	2	3	3	3	3	4	4
platelet	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 28: Highest toxicity of all blood elements

1) Hemoglobin:

Highest Toxicity Graded	Frequency	Percentage
0	8	40
1	4	20
2	5	25
3	2	10
4	1	5

Table 5: Incidence and grading of hemoglobin toxicity

2) Leucocyte count

Highest Toxicity Graded	Frequency	Percentage
0	11	55
1	7	35
2	2	10
3	0	0
4	0	0

Table 6: Incidence and grading of leucocyte toxicity

3) Neutrophil count

Highest Toxicity Graded	Frequency	Percentage
0	14	70
1	5	25
2	0	0
3	1	5
4	0	0

Table 7: Incidence and grading of granulocyte toxicity

4) Lymphocyte count

Highest Toxicity Graded	Frequency	Percentage
0	0	0
1	1	5
2	4	20
3	11	55
4	4	20

Table 8: Incidence and grading of lymphocyte toxicity

5) Platelet count

Highest Toxicity Graded	Frequency	Percentage
0	19	95
1	0	0
2	0	0
3	1	5
4	0	0

Table 9: Incidence and grading of platelet toxicity

Grade 3 or more toxicity

When only grade 3 or more toxicity was considered the following were noted:

Grade 3 or more toxicity	Frequency	Percentage
Hemoglobin	**3**	**15**
Leucocytes	**0**	**0**
Neutrophils	**1**	**5**
Lymphocytes	**15**	**75**
Platelets	**1**	**5**

Table 10: Incidence of grade 3 or more toxicity among all blood elements

Hemoglobin:

Using the Two-sample Wilcoxon rank sum (Mann-Whitney) test it was found that Grade 3 or higher Hemoglobin toxicity had a significant correlation to the V30 and V40 values (Prob>Z=0.0229 and 0.0095;respectively)

There was however no correlation with the V5, V10 and V20 values

Leucocytes (Total WBC count)

None of the patients in the study experienced grade 3 or higher toxicity.

Two patients experienced grade 2 toxicity.

None of the patients received any growth factor support during the course of neoadjuvant chemoradiotherapy

There was, however no correlation between the incidences of grade 2 leucopenia with any of the dosimetric parameters studies.

Granulocytes(Absolute neutrophil count)

One patient experienced grade 3 or more toxicity. No statistical analyses could be performed using the dosimetric analyses for this patient

Lymphocytes(Absolute lymphocyte count)

15 patients experienced grade 3 or more toxicities. The two-sum Wilcoxon test revealed no significant correlation between the incidence and the values of the dosimetric variables.

Platelets

One patient experienced grade 3 or more toxicity. The variables could however, not be analyzed for statistical purposes.

Pre and post RT Volumes of bone marrow on MRI

ID No	Pre RT volume in cc	Post RT volume in cc	
1	405.98	115.78	71.48
2	390.48	112.47	71.19
3	389.69	175.15	55.05
4	309.92	167.14	46.17
5	451.07	236.9	47.48
6	404.58	77.9	80.74
7	52.54	29.72	38.98
8	208.94	60.69	70.95
9	367.28	205.09	44.15
10	423.87	70.38	83.39
11	248.89	71.59	71.23
12	246.29	135.61	44.93
13	180.6	56.22	68.87
14	325.15	160.07	50.77
15	286.94	117.11	59.68
16	317.26	115.25	63.67
17	382.47	221.23	42.15
18	498.58	221.41	55.59
19	262.4	NA	NA
20	436.78	NA	NA

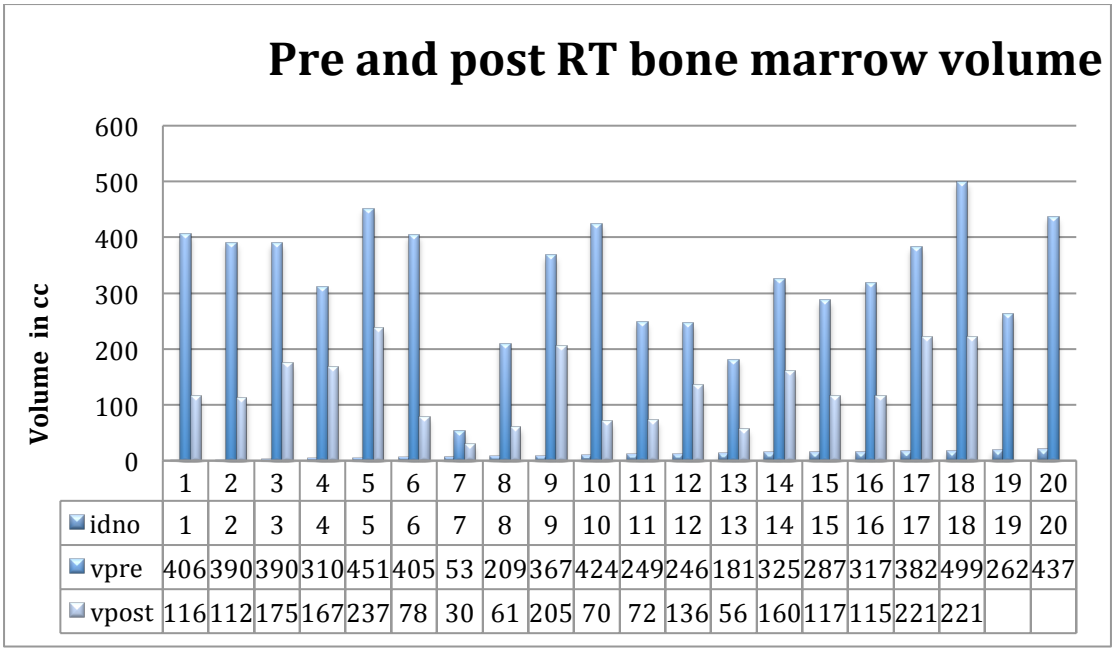
Table 11: Pre and post chemoradiotherapy volumes of active bone marrow as seen on the MRI; Percentage inactivation of active marrow.

As a part of the secondary objective of the study we tabulated the volumes of the active bone marrow as visualized on the MRI, both prior and after neo adjuvant chemoradiotherapy.

Univariate analysis showed the following:

Pre neo adjuvant chemoradiotherapy: The volume of active marrow as visualized on the MRI had a median value of 346.21 cc ranging between a maximum and minimum value of 52.54cc to 498.58cc respectively.

Post neo adjuvant chemoradiotherapy: The volume of active marrow as visualized on the pre operative MRI had a median value of 116.44cc ranging between a maximum and minimum value of 29.72cc and 236.90cc respectively.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
idno	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
vpre	406	390	390	310	451	405	53	209	367	424	249	246	181	325	287	317	382	499	262	437
vpost	116	112	175	167	237	78	30	61	205	70	72	136	56	160	117	115	221	221		

Figure 29: Graphical representation of pre and post therapy active marrow volumes

Percentage inactivation

The percentage inactivation of active marrow that occurs following completion of neo adjuvant chemoradiotherapy was also calculated for all patients.

It was noted to have a median value of 57.64% ranging between 38.98% to 83.39%

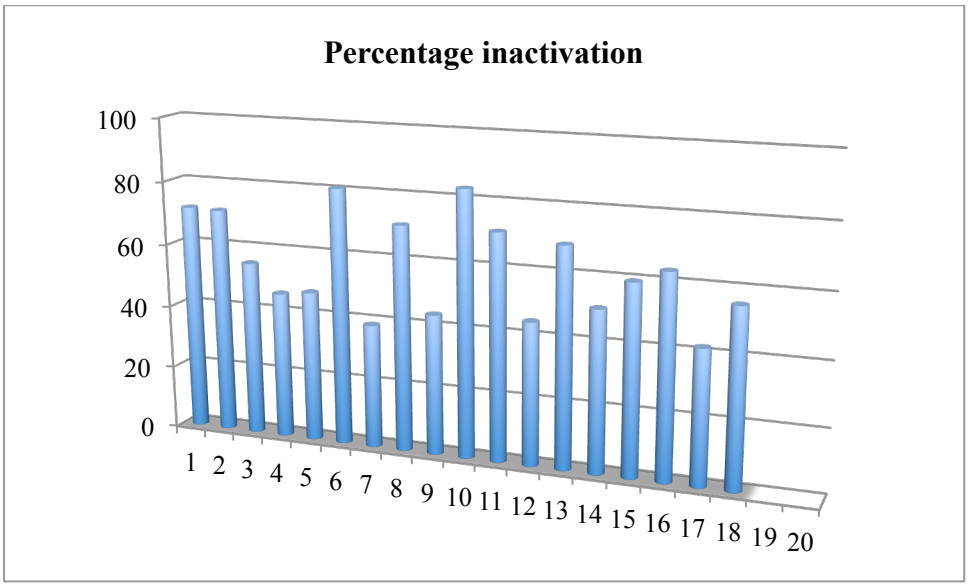


Figure 30: Graphical representation of the percentage inactivation of active marrow.

A paired T test was applied to verify the differences noted between the pre and post treatment values.

The mean of the pre treatment value was 327.25cc with a 95% CI between 272.71 – 381.78cc

The mean of the post treatment value was 130.53 cc with a 95% CI between 98.86 – 162.21cc

The result was highly significant with a p value < 0.0001

Efforts were made to review the values of the active marrow contoured on the MRI as well as that of the whole pelvis on the CT.

There was no correlation between the V5 values and the volume of active marrow on the pre treatment MRI

The V20 showed a correlation that was marginally significant with the volume of the active marrow on the post treatment MRI(p value=0.0464)

Discussion

Though the incidence of colorectal cancer in India is well below that of other developed countries, it is of particular concern to oncologists in our country in view of the increasing trends (1) (91). Due to the lack of screening programs in our country, most of the patients in our country also present with locally advanced disease. The benefit of pre operative chemoradiotherapy in improving local control has been verified by several trials (60) (63).Neo adjuvant long course chemoradiotherapy followed by TME is the present standard of care for patients with locally advanced disease.

Bone marrow is exquisitely sensitive to both radiotherapy and chemotherapy (89). The distribution of the active marrow in the adult in the region of the pelvis, proximal femurs and the lumbosacral spine is close to 51% (92).The additive toxicity of radiotherapy and chemotherapy on bone marrow and its clinical implications has been well recognized and appreciated in gynaecological malignancies (84). Efforts are being made to decrease the toxicity by adopting different radiotherapy techniques. Conformal radiotherapy or Intensity modulated radiotherapy offers the possibility of sparing bone marrow, while not compromising on the dose delivered to the target volume. The advantages of 'Bone marrow sparing IMRT' has been shown by several groups in the areas of anal and gynaecological malignancies (80) (93) (87)(84) (85). Similar studies for rectal cancer have not been commonly undertaken. The possibility and the advantages of a marrow sparing technique in rectal cancer would be of immense benefit to the patient as well as the treating Oncologist.

Due to the paucity of any formal assessments of bone marrow toxicity in rectal cancer patients, this study was undertaken. It is also a well known fact the contouring of the entire pelvis on the planning CT as a surrogate for delineating the active

marrow is a gross over estimate (82) (88).It was therefore decided to delineate the marrow on the T1-w images on both the pre radiotherapy as well as the post radiotherapy MRI's.

The objectives of the study were to correlate the dose received by the pelvis with the incidence and degree of hematological toxicity. As a part of the secondary objective, we sought to get an estimate of the percentage inactivation of the bone as a result of chemoradiotherapy, as seen on the MRI.

We found that the incidence of grade 3 or more toxicity of hemoglobin correlated with V30 and V40 values. The toxicity grades of the other blood elements however did not show any correlation with any of the dosimetric variables.

The conversion of active red to inactive yellow marrow as a result of the inactivation of the marrow that follows chemoradiotherapy along with the correlation of their associated variables were found to be significant.

We faced some shortcomings associated with the study. In retrospect, we realize that ours is a relatively small sample size and generalization of the results to the entire cohort of rectal cancer patients would be a premature attempt to do so. Due to the slow accrual and paucity of time we had to include both retrospective as well as a prospective group of patients. Another limitation was that we had a relatively short follow up of hematological toxicity. The implications of bone marrow toxicity on the clinical course of patients and its correlation to oncological outcomes could not be completed. Also, we noted that the contouring of the bone marrow on the T1-w MRI images is heavily observer dependent. There are no formal guidelines or protocols that could have helped in better objective delineation of the bone marrow.

The toxicity on the bone marrow due to the additive insults of chemotherapy and radiotherapy is by no means insignificant. Some of the recent developments in radiotherapy planning and delivery offer the advantage of sparing or limiting the dose to the organs at risk, while not compromising on the dose delivered to the target volumes. One such technique is the use of Bone marrow sparing IMRT, which has shown to be of benefit in gynaecological and anal malignancies. The adoption of IMRT in the treatment of rectal cancer, however, is still not widespread. It is hoped that with the development of better functional imaging to aid in radiotherapy planning, the implications of bone marrow toxicity and the possibility of limiting the same using IMRT, will be recognized. More studies to correlate the grade toxicity with dose, to correlate the degree of toxicity with both oncological and non-oncological treatment outcomes, are needed. The need for prospective study groups with an adequately long follow up would be required to fully appreciate the possibilities, the advantages and the limitations that these techniques offer.

In spite of the above limitations, it is hoped that the present study translates into a small step taken in that direction.

Conclusion

The volume of pelvic bone marrow receiving atleast 30Gy or more in patients undergoing long course chemoradiotherapy for locally advanced rectal cancer has a significant impact on anemia. There was also a significant conversion of active to inactive bone marrow as detected on the MRI.

Due to the significant myelosuppression associated with the use of both chemotherapy and radiotherapy in the management of rectal cancer, efforts to limit the toxicity to the bone marrow must be undertaken. The paucity of data relating to and formally assessing the degree of bone marrow inactivation as a consequence of chemoradiotherapy warrants the need for further studies in this direction. The use of MRI and other functional imaging for visualization and delineation of the bone marrow and its use in radiotherapy planning is now providing possibilities to further limit normal tissue toxicity.

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Enclosures

INFORMED CONSENT

Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemoradiation for Locally advanced Rectal cancer

INFORMED CONSENT

Sl Number:

Participant ID: Date:

Participant name: Hospital Number:

I Mr/Mrs ……,Son/Daughter of…….. Hospital number …… have been explained in a language that I clearly understand about the nature of the condition and its associated prognosis.

The options,the benefits of the proposed line of treatment and the side effects have been clearly explained to me.The costs associated with treatment have also been mentioned.

The aim,the methods of collection and usage of the data,the proposed end points have been clearly explained to me by ……

I am aware that the data collected from my participation in this study,will be utilized for correlating and estimating the degree of myelosuppression caused during the process of my treatment.

I am aware that my participation in this study is entirely voluntary.

I am also aware that I may,at any time of the study,seek more information regarding the same.I may wish to withdraw from the study at any point,after suitable intimation,for reasons that I may not be willing to share.

I hereby give my fully informed consent for participation in the study.My consent has been given under my own free will and under no undue or external coercion.

PARTICIPANT	WITNESS
NAME IN CAPITALS:	NAME IN CAPITALS:
SIGNATURE:	SIGNATURE:
THUMB IMPRESSION:	THUMB IMPRESSION:

PLACE:

ADDRESS AND CONTACT NUMBER:

DATE AND TIME:

INVESTIGATOR'S NAME AND SIGNATURE

DATE:

PARTICIPANT INFORMATION SHEET

Correlation of Dose to Bone Marrow with Hematological toxicity AND

MRI based estimation of conversion of active to inactive bone marrow in Long course Chemoradiation for Locally advanced Rectal cancer

Locally advanced rectal cancer continues to be a major global burden. Though the problem of colorectal cancer was comparatively lower in India until now,it looks like there will be an increase in the number of people who will be suffering from this disease in the future,due to changes in diet and lifestyle.

The treatment of locally advanced rectal cancer is one that involves 3 different oncology specialties;radiotherapy,chemotherapy and surgery.One of the most accepted lines of management is to start with radiotherapy along with chemotherapy (with capecitabine).The aim is to reduce the tumour size so that the surgery may be be more complete.Surgery is usually carried out 4-6 weeks after completion of radiotherapy and chemotherapy.Following completion of surgery,further chemotherapy is usually given to reduce the number of tumour cells that may be left behind.

Bone marrow which are the regions in the body where production of blood cells occurs,are usually located in the lower back,the hip bone and the upper thighs.

Both radiotherapy and chemotherapy,though meant to act on the cancer cells,have side effects caused due to their effects and destruction of normal cells.Radiotherapy and chemotherapy,both have effects on the bone marrow causing reduction in the production of the blood cells.This is reflected in the drop in the blood counts which will be checked every week during treatment.

The effects of chemotherapy on the bone marrow can be modified by changing the dose of the drug given.But the effect of radiotherapy causing the bone marrow toxicity has not been documented clearly.

The main aim of this study is to find out how much additional damage is being caused by radiotherapy. We are trying to correlate the dose received by the hip bone with the degree of bone marrow toxicity. We will be trying to estimate how much of the bone marrow is being destroyed during the course of treatment(using MRI scan)

We would like to point out that though there are no immediate benefits to the participants of the study.But,with the data that will be collected,it is hoped,that we will be able to find out a dose to the bone marrow below which the degree of bone marrow toxixity will be very less(compared to the benefits that may be obtained).This may be beneficial in future where we will try and restrict the dose to the bonemarrow so that more people complete the treatment that was intended.

The proposed study involves no additional expenses to be borne by you. The cost asscociated with the treatment would remain the same.

Your participation in the study is entirely voluntary and you may wish to withdraw from the same at any point. However in case of withdrawal,the data collected thus far may be used in the analysis in order to try and come to a conclusion.I assure you that your personal details will not be revealed at any point in this study.

Your participation in this study will help doctors make better decisions in the future.

Your participation will be deeply appreciated.

Thank you for your interest and your valuable time

Please feel free to contact me for any further details that you may wish to obtain

Dr Jayant J Bhargav

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PATIENT INFORMATION SHEET IN TAMIL

பங்கேற்பவரின் தகவல் அறிக்கை

மலக்குடலில் ஏற்படும் புற்றுநோய் ஒரு பெரிய உலக அமையாக இருந்து வருகிறது. பெருங்குடல் புற்றுநோய் இந்தியாவை பொருத்த அளவில் குறைந்தே காணப்பட்டது. எனினும் வரும் காலத்தில் உணவு மற்றும் வாழ்க்கை முறை மாற்றம் காரணமாக இதன் அதிகரிப்பு இருக்கக்கூடும்.

மலக்குடலில் ஏற்படும் புற்றுநோய் சிகிச்சை 3 வகை புற்று நோயியால் சிகிச்சை முறைகளை கொண்டது. 1. கதிரியக்க சிகிச்சை, 2. கீமோதெரபி, 3. அறுவை சிகிச்சை. இவற்றில் சிறந்த வகை சிகிச்சை முறை என கருதப்படுவது கதிரியக்க சிகிச்சையுடன் இணைந்து கீமோதெரபி (கேப்சிடபின்) கொண்டு புற்று நோயினை குறைத்த பின்னர் அறுவை சிகிச்சை கொண்டு சிகிச்சை அளிக்கும் முறை. அறுவை சிகிச்சை பின்னர் மீண்டும் கீமோதெரபியின் மூலம் மீதம் உள்ள புற்றுநோய் உயிரனுக்களின் எண்ணிக்கையை குறைக்கும் முறை கையாளப்பட்டு வருகிறது.

முதுகு, இடுப்பு மற்றும் மேல் தொடையில் உள்ள எலும்பு மஞ்சையால் இரத்த அணுக்கள் உற்பத்தியாகும். கதிரியக்க மற்றும் கீமோதெரபி சிகிச்சை முறை புற்றுநோய் அணுக்களை அழிக்க அளிக்க பட்டவை, எனினும் அதன் பக்க விளைவாக இரத்த அணுக்கள் குறையும் வாய்ப்பு உள்ளது. இதனை கண்டறிய வாரம் ஒருமுறை இரத்த பரிசோதனை செய்யப்படும்.

இரத்த அணுக்கள் குறையாமல் இருக்க கீமோதெரபியின் அளவினை குறைத்து செலுத்தலாம். எனினும் கதிரியக்க சிகிச்சையால் ஏற்படும் இரத்த அணுக்களின் குறைவின் அளவு கண்டறியப்பட்டதில்லை.

இந்த ஆய்வின் முக்கிய நோக்கம் கதிரியக்க சிகிச்சையால் ஏற்படும் மஞ்சை நச்சுத்தன்மையை கண்டறிவதாகும். இடுப்பு எலும்பில் கதிரியக்க தாக்கத்தால் ஏற்படும் மஞ்சை நச்சுத்தன்மையினை ஒப்பிட்டு பார்கின்றோம். கதிரியக்க சிகிச்சையின் இடையில் எம்.ஆர்.ஐ ஸ்கேன் மூலம் இடுப்பு எலும்பு மஞ்சையின் தாக்கத்தை தெரிந்து கொள்கிறோம். இந்த ஆய்வினால் பங்கேற்பாளர்க்கு உடனடி பயன்கள் எதுவும் இல்லை.

எனினும் இந்த ஆய்வினால் மஞ்சை நச்சுத்தன்மை ஏற்படும் கதிரியக்க அளவினை கண்டறிவதன் மூலம், பிற்காலத்தில் கதிரியக்க அளவினை குறைத்து செலுத்தி முழுசிகிச்சையினை இவ்வகை நோயாளிகளுக்கு அளிக்க முடியும்.

இந்த ஆய்வினால் உங்களுக்கு எந்த கூடுதல் செலவும் ஏற்படாது உங்கள் சிகிச்சை முறைக்கு ஏற்படும் செலவும் ஏற்படாது உங்கள் சிகிச்சை முறைக்கு ஏற்படும் செலவே உங்களிடம் இருந்து பெறப்படும்.

ஆய்வில் உங்கள் பங்களிப்பு முற்றிலும் உங்கள் தன்னார்வத்திற்கு உற்பட்டது. எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து நீங்கள் விலகிக் கொள்ளலாம். எனினும் ஆய்வில் அதுவரை உங்களிடமிருந்து சேகரிக்கப்பட்ட தரவு விவரங்கள் பயன்படுத்தப்படும்.

உங்களின் தனிப்பட்ட விவரம் இந்த ஆய்வில் எந்த தருனத்திலும் வெளியிடப்படாது. இந்த ஆய்வில் நீங்கள் பங்கேற்பினால் மருத்துவர்கள் எதிர்காலத்தில் நல்ல முடிவுகள் எடுக்க உதவும். உங்கள் பங்கு ஆழமாக பாராட்டப்படுகிறது. உங்கள் ஆர்வத்திற்கும் விலைமதிப்பற்ற நேரத்தினை இந்த ஆய்வில் அளித்ததற்கு எங்களின் மனமார்ந்த நன்றி.

நீங்கள் மேலும் விவரங்களை பெற விரும்பினால் என்னை தொடர்பு கொள்ளவும்.

PATIENT INFORMATION SHEET IN HINDI

सहभागी ("प्रतिनिधी सूचना प्रति")

"सहभागी सूचना पत्र"

किसी जगह पर ज्यादा बढ़ा हुआ या फैला हुआ (स्थानिक ग्रसित) गुदा कैंसर रोग (Rectal Cancer) लगातार (निरंतर) समूर्ण विश्व के लिये एक बहुत बड़ी चिंता का कारण हो सकता है। हालांकि बड़ी ग्रंतड़ी का निचला भाग का कैंसर रोग (Colorectal Cancer) भारत में ग्रामीण तक तुलनात्मक रूप से कम है, ऐसा दिखाई पड़ता है कि भविष्य में संभवतः मनुष्यों में इसकी संख्या (गिनती) में बढ़ोतरी (ज्यादा) होगी जो इस विमारी के द्वारा ग्रसित (लक्षणीय) है, इसका पिछले 2021 का उनके स्वास्थान एवम् रहन सहन में परिवर्तन हुई है।

(खास) विशेष जगह पर ज्यादा फैला हुआ गुदा कैंसर रोग (Rectal Cancer) का इलाज या उपचार, (3) तीन ग्रेलरा (विधिनां) विशेष (खास) पद्धति। तरीके से किया जाता है; रेडियो थेरापी, कीमो थेरापी ग्रौर सर्जरी (शल्यक्रिया)। इसमें से सबसे ज्यादा सुचारू रूप से ग्रथवा उपयोगी तरीके से रेडियो थेरापी (Radio Therapy) के साथ-साथ कीमो थेरापी ग्रौर साथ में Capecitabine के साथ उपचार (इलाज) प्रारंभ (शुरु) किया जाता है। इसका उद्देश्य (aim) गाँठ के ग्राकार (Tumour Size) को कम करना है ताकि शल्यक्रिया (Surgery) ज्यादा उपयोगात्मक पूर्ण (पूरी) हो सके। रेडियो थेरापी (Radio Therapy) ग्रौर कीमो थेरापी (Chemotherapy) पूर्ण होने पर, लगभग (सामान्यतया) 4-6 हफ्ते के बाद शल्यक्रिया (Surgery) की जाती है। शल्यक्रिया (Surgery) पूर्ण ग्रथवा पूरा हो जाने पर, ग्रागे चलकर ग्रावश्यकतानुसार उपयोगितानुसार या ग्रावश्यकतानुसार कीमो थेरापी (Chemotherapy) दी जाती है ताकि गाँठ के ग्रंश (टुकड़ा) (Tumer Cells) जो छूट या बच गये हैं उन्हें कम या घटाया जा सके

Bone marrow ये शरीर में पाये जाने वाले वे (ऐसे) स्थान या जगह हैं जहां Blood cells का उत्पादन पाया जाता है, जोकि साधारणतया या अक्सर तौर से Lowerback (कमर के नीचे), Hip bone (पुट्ठों की हड्डी) और ऊपरी जांघ (Upper thighs) के हिस्सों (स्थानों) या जगहों में पाया जाता है या स्थित रहता है।

दोनों रेडियो थेरापी और कीमो थेरापी का हानिकारक मकसद (उद्देश्य) कैंसर रोग की कोशिकाओं पर नष्ट करना/कार्य करना प्रभावी प्रभाव डालना है, पर इसके विपरीत प्रभाव (परिणाम) भी हैं जो कि इसके साधारण पेशियों को नष्ट करने के प्रभाव से होते हैं। रेडियो थेरापी और कीमो थेरापी दोनों का Bone marrow पर असर (प्रभाव) होता है जिसके कारण Blood cells (रक्त कोशिकाओं) की उत्पादकता बढ़ने में (कमतरता) कमी या घटी होती है। यह Blood count कम होने में अथवा नीचे गिरने में (क्रियाशील) प्रभावित होता है, जिसे या इस की उपचार या इलाज के समय (हर) प्रत्येक सप्ताह जाँच या परिक्षण करना चाहिये।

Bone marrow पर कीमो थेरापी के दुष्प्रभाव (बुरा असर) को दी जाने वाली दवाई की मात्रा को बदलकर सुधारा जा सकता है। लेकिन Radio Therapy के प्रभाव को जिसके कारण Bone marrow की विधायकता (जहरीलापना) समा जाता है, इसकी स्पष्टता या सत्यता कहीं भी दुरुपयोगात्मक या विपरीत रूप से स्पष्ट (clearly) नहीं पाई गई है।

इस प्रयास या शोधन प्रदर्शन का मुख्य ध्येय या उद्देश्य यह है कि रेडियो थेरापी के कारण कितना अतिरिक्त नुकसान हो सकता है या हुआ है, यह मालूम करना या जानना है। हम यह कोशिश कर रहे हैं कि जो मात्रा (खुराक)

Bone marrow की विषाक्तता (जहरीलापन) के स्तर या श्रेणी के साथ कूल्हे की हड्डी (Hip bone) के द्वारा प्राप्त होती है उसका समन्वय (सहसम्बन्ध) किया जा सके। हम यह कोशिश करेंगे कि प्रोक्लेम या दिखावा करने के बाद निश्चित करेंगे कि इलाज के दौरान Bone marrow कितना नष्ट हुआ। (Using MRI Scan)

हम यहाँ बताना चाहेंगे या यह जानकारी देना चाहेंगे कि हालाँकि प्रत्यास करने वाले सहभागी (प्रतिनिधी) को दूसरे पुरुषन लाभ या फायदा तो नहीं होगा, लेकिन जो जानकारी या विवरण इकट्ठा या मालुम किया गया है, यह ग्राशा (उम्मीद) की जाती है कि हम इस योग्य (काबिल) हो सकेंगे ताकि जाना सके या ढूंढ सके उस मात्रा या खुराक को जो Bone marrow को ~~निचले स्तर या कम से कम~~ ~~या सके जिससे~~ नीचे ला सके या कम कर सके जिससे Bone marrow Toxixity का स्तर या प्रमाण सबसे कम हो जाये (उन फायदों की तुलना में जो हमने प्राप्त किये हैं।

ग्राफ़ो चलकर भविष्य में यह फायदेमंद हो सकता है, जहाँ पर हम कोशिश करेंगे कि दवाई की मात्रा या खुराक मरीज पहले कम हो Bone marrow के लिये लेकिन ग्रधिक से ग्रधिक लोग या मरीज Partial उपचार या इलाज को पूरा कर सके जो योजनाबद्ध या ग्रावश्यकतानुसार (intended) तैयार किया गया या सुनिश्चित किया गया है।

इस ~~प्रत्यास~~ या जानकारी के लिये जो योजना पेश की गई है उसके लिये ग्रतिरिक्त ~~ग्रतिरिक्त~~ खर्च ~~इसमें~~ शामिल नहीं है। ग्रगला ग्राफ़ को कोई ~~ग्रतिरिक्त~~ ग्रतिरिक्त खर्चा नहीं करना है। इलाज से सम्बन्धित खीनत या खर्चे बेसहारा सहारा रहेगा।

अध्ययन करने या जानकारी प्राप्त करने के लिये आपका सहभाग या प्रतिनिधीत्व अपेक्षित। इसमें हिस्सा लेना पूर्ण रूप से या पूरी तरह से इच्छा या स्वयं की इच्छा (मर्जी) पर है, और आप किसी भी समय यदि चाहते हैं तो किसी भी स्थान पर अपनी सहभागिता से हट सकते है या वापस हो सकते हैं, चौथी या फिर भी पीछे लेने या हटने की दशा में परिस्थिती में, जो जानकारी या विवरण प्राप्त किये गये या इकट्ठा किये गये हैं उन्हें विश्लेषण से किसी तत्व के परीक्षण (Analysis) के लिये प्रयोग या इस्तेमाल किया जा सकेगा कोशिश या अनुमान के लिये लेकिन किसी निर्णय पर पहुंचा जा सके मैं आपको आश्वासन (भरोसा) दिलाना चाहता हूँ कि आपके व्यक्तिगत विवरण किसी भी केस या स्थान पर इस अध्ययन या जानकारी के बारे में प्रकाशित या बतलाये नहीं जायेंगे।

DATA COLLECTION SHEET `

CHRISTIAN MEDICAL COLLEGE, VELLORE

Correlation of Dose to Bone Marrow with Hematological toxicity AND MRI based estimation of conversion of active to inactive bone marrow in Long course Chemo- radiation for Locally advanced Rectal cancer

Case Record Form – 1
Demographic and Clinical Details

ID NO | Date of Birth (dd mm yyyy) | Hospital Number | Recruitment date (dd mm yyyy)

RT No | Telephone No | Email]

NAME — Last | Middle | First

Sex (1=male 2= female) ……

Marital Status (1= unmarried 2= married) ……..

Occupation (1=skilled; 2=unskilled)……..

Location of growth
1.Upper
2.Middle
3 Lower ……..

Anorectal involvement/Circumferential involevemnt (1=Yes 2=No)

T status (1=T1;2=T2; T3=3; T4=4)……

N Status (1=N1; 2=N2; 3= N3) ……..

GENERAL EXAMINATION

ECOG Performance status ……..

0 =Fully active, able to carry on all pre-disease performance without restriction
1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2= Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3= Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4= completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5= Dead

Height (in cm) ……

Weight (in Kg) …… ……..

BODY SURFACE AREA (per square metre)……

PULSE RATE…….. BLOOD PRESSURE……

Systemic Examination:

Cardiovascular:

Respiratory:

Gastrointestinal:

Neurological:

Digital Rectal Examination

Proctosigmoidoscopy

Colonoscopy

	HEMOGLO	TC	ANC	LYMPHOCYTE	PLATELET COUNT	TOXICITY
WEEK 0						
WEEK 1						
WEEK 2						

WEEK 3						
WEEK 4						
WEEK 5						
WEEK 6						

HIGHEST TOXICITY GRADED: ☐

TREATMENT BREAKS DURING RT: (1=Yes 2=No) ☐

DURATION: ☐

REASON:

BREAKS WITH CONCURRENT CHEMOTHERAPY: (1=Yes 2=No) ☐

DURATION: ☐

REASON:

	V5	**V10**	**V20**	**V30**	**V40**
VOLUME MARROW					

VOLUME OF MARROW PRIOR TO NEO ADJUVANT CHEMORADIOTHERAPY: ☐

VOLUME OF MARROW POST NEO ADJUVANT CHEMORADIOTHERAPY: ☐

PERCENTAGE INACTIVATION: ☐

Date: __/___/_____ Investigator's Signature:_____